American Journal of Diseases of Children

VOLUME 77 FEBRUARY 1949 NUMBER 2

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INFLUENZA VACCINE

A Study of Serologic Responses and Incidence of Reactions Following Subcutaneous and Intradermal Inoculation

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ALTHOUGH in recent years infection with the viruses of influenza has not produced serious illness the rates of attack during epidemics, affecting all age groups, are of major concern to the practicing physician. A procedure capable of producing active immunity against influenza is therefore desirable. Moreover, such a procedure should not be accompanied with a high incidence of undesirable reactions, since the disease itself has generally not been of serious consequence.

There has been ample demonstration since 1937 [1] that the influenza virus in a variety of preparations may be used to induce in human beings a rise in humoral antibody. Combined type A and type B vaccine prepared from chorioallantoic fluid of chicken embryo was given extensive trial by the Commission on Influenza of the United States Army during an epidemic of type A influenza in 1943 [2] and

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This paper was presented in part at the annual meeting of the Western Society for Clinical Research, San Francisco, Nov. 8, 1947.

From the Infectious Disease Laboratory of the San Francisco Hospital. This laboratory is supported by the Division of Medicine and Pediatrics of the University of California Medical School and by the Department of Public Health of the City and County of San Francisco.

1. Francis, T., Jr., and Magill, T. P.: The Antibody Response of Human Subjects Vaccinated with the Virus of Human Influenza, J. Exper. Med. **65**:251-259 (Feb.) 1937.

2. Rickard, E. R.; Thigpen, M. P., and Crowley, J. H.: Vaccination Against Influenza at the University of Minnesota, Am. J. Hyg. **42**:12-20 (July) 1945. Hale, W. M., and McKee, A. P.: The Value of Influenza Vaccination When Done at the Beginning of an Epidemic, ibid. **42**:21-27 (July) 1945. Eaton, M. D., and Meiklejohn, G.: Vaccination Against Influenza: A Study in California During the Epidemic of 1943-1944, ibid. **42**:28-44 (July) 1945. Hirst, G. K.; Plummer, N., and Friedewald, W. F.: Human Immunity Following Vaccination with Formalinized Influenza Virus, ibid. **42**:45-56 (July) 1945. Salk, J. E.;

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was shown to have protective effect. This effect, however, varied in magnitude throughout the areas under study. Similar vaccines have appeared to have an even more strikingly protective effect against type B influenza during two epidemics in 1945.[3] While this combined vaccine at its present stage of development can be said to offer a reduction in case incidence of influenza during an epidemic, the protection afforded has been definitely less than that gained from a number of the more commonly used immunizing agents.

Investigations on the effectiveness of this combined vaccine in children have not been reported, and its use in children at present has been based on the results obtained in adults. There is evidence that children react more severely to the vaccine when it is injected subcutaneously. Grant[4] reported on the local and systemic reactions in a group of 16 children, aged 13 months to 8 years, who were given from 0.25 to 1 cc., approximately according to age. He concluded that febrile reactions were more frequent than in adults and, from his series, that the 0.5 cc. dose produced reactions comparable to those seen in adults given 1 cc. of vaccine. He suggested repeating this dose in two weeks to increase the immunity. No data on the antibody response were presented.

The intradermal route of inoculation as a method of immunization was first suggested in 1931 by Tuft,[5] who used typhoid vaccine in this way, with good antibody responses. It has been repeatedly confirmed since that time that this method produces as good an antibody response as the subcutaneous route not only in immunization against typhoid but also in the use of scarlet fever toxoid[6] and diphtheria toxoid.[7] The reports on the intradermal use of immunizing agents have stressed the decided decrease in severity and incidence of systemic reactions as

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Menke, W. J., Jr., and Francis, T., Jr.: A Clinical Epidemiological Evaluation of Vaccination Against Epidemic Influenza, ibid. **42**:57-93 (July) 1945. Magill, T. P.; Plummer, N.; Smillie, W. G., and Sugg, J. Y.: An Evaluation of Vaccination Against Influenza, ibid. **42**:94-105 (July) 1945.

3. Francis, T., Jr.; Salk, J. E., and Brace, W. M.: Effect of Vaccination Against Epidemic Influenza B, J. A. M. A. **131**:275-278 (May 25) 1946. Hirst, G. K.; Vilches, A.; Rogers, O., and Robbins, C. L.: The Effect of Vaccination on the Incidence of Influenza B, Am. J. Hyg. **45**:96-101 (Jan.) 1947.

4. Grant, H. B.: Influenza Virus Vaccine: Local and Systemic Reactions in Children, J. Pediat. **29**:485-486 (Oct.) 1946.

5. Tuft, L.: Active Immunization Against Typhoid Fever, with Particular Reference to an Intradermal Method, J. Lab. & Clin. Med. **16**:552-556 (March) 1931.

6. Robinson, J. H.: Active Immunization to Scarlet Fever by the Intracutaneous Method, J. Immunol. **31**:373-375 (Nov.) 1936.

7. Kern, R. A.; Crump, J., and Cope, T. A.: Diphtheria Immunization of Allergic and Non-Allergic Individuals by Intracutaneous Injection of Alum-Precipitated Toxoid, J. Allergy **6**:525-531 (Sept.) 1935.

compared with the subcutaneous method. It was also emphasized[7] that the use of this route with diphtheria toxoid is of special advantage in persons with allergies and reduces the frequency of unfavorable reactions, either local or general.

The intradermal route was applied in the use of combined type A and type B influenza vaccine by investigators in the United States Navy,[8] who concluded that the antibody response in adults from 0.1 cc. given intradermally was as good as that from 1 cc. given subcutaneously. The systemic reactions after intradermal inoculation occurred only one third as frequently as those from the subcutaneous inoculation, and the local reactions were similarly reduced.

The problem of allergy to the variety of virus and rickettsial vaccines now available has been given a great deal of attention in the last three years. Ratner and Untracht[9] reviewed the subject and investigated the problem of allergy to influenza type A and B vaccine in children. They expressed the opinion that allergic reactions to such vaccine are of the nature of allergy to egg protein, which is present in the vaccine. In a group of 108 highly allergic children, they found that 10.2 per cent were sensitive to egg protein but only 4.6 per cent showed sensitivity sufficient to be regarded as a potential hazard in administration of influenza vaccine. They urged preliminary intradermal testing with 0.02 cc. of undiluted vaccine and suggested the use of epinephrine simultaneously with the vaccine with those children who showed a moderate local reaction. They stated the belief that the general constitutional reaction to influenza vaccine, which included fever, chills and malaise, was the reaction to the injection of a foreign protein. They found no child who reacted positively to the test dose of vaccine who did not also react positively to egg white.

The present investigation was undertaken to determine, if possible, what subcutaneous doses were required to produce an effective antibody response, whether a satisfactory response could be obtained with the use of the intradermal route and, finally, whether any method of inoculation produced substantial serologic response without undue reaction.

MATERIAL

A group of children hospitalized for childhood tuberculosis was chosen for study. These patients were selected because they were available for long term follow-up study and, at the same time, were under careful nursing supervision. Except for

8. Van Gelder, D. W.; Greenspan, F. S., and Dufresne, N. E.: Influenza Vaccination: Comparison of Intracutaneous and Subcutaneous Methods, U. S. Nav. M. Bull. **47**:197-206 (Jan.-Feb.) 1947.

9. Ratner, B., and Untracht, S.: Allergy to Virus and Rickettsial Vaccines: I. Allergy to Influenza A and B Vaccine in Children, J. A. M. A. **132**:899-905 (Dec. 14) 1946.

2 children with bone involvement, all had pulmonary disease. Those selected for study were without serious complication, and their temperature records varied to a minimal degree from those of normal children. Two children were included who were in the hospital for physical therapy following acute anterior poliomyelitis. The age range of the children studied was from 1 to 14 years (table 1).

Specimens of blood were drawn on the day before vaccine in any form was given. Postvaccination specimens were drawn twelve to sixteen days after the initial vaccination, and a sampling of children was tested one month after vaccination. The blood was collected in sterile tubes and the serum separated immediately and stored at 4 C.

The vaccine used for the children was combined type A and type B influenza virus vaccine.[10] This vaccine was prepared from the allantoic fluid of 12 day chicken embryos which had been incubated for forty-eight hours after inoculation with the influenza virus. The virus was separated from the fluid by adsorption on chicken red blood cells, agglutination at low temperature and elution in isotonic

TABLE 1.—*Number of Children in Each Age Group Correlated with Method of Inoculation*

Age Group, Years	Method of Inoculation			
	Subcutaneous Route	Intradermal		All Routes and Doses
		0.1 Cc.	0.2 Cc.	
1 to 2	0	3	2	5
2 to 3	1	2	3	6
3 to 4	3	8	2	13
4 to 5	3	2	2	7
5 to 6	3	3	1	7
6 to 7	2	3	1	6
7 to 8	0	2	2	4
8 to 9	1	1	3	5
9 to 10	1	3	2	6
10 to 11	6	1	2	9
11 to 12	3	0	1	4
12 to 13	2	1	0	3
13 to 14	0	1	1	2
14 to 15	2	0	0	2
Average age	7.85	4.99	6.18	6.34

sodium chloride U. S. P. solution. The vaccine contained solution of formaldehyde U. S. P. (0.1 per cent) and a 1:1,000 concentration of "merthiolate". In this vaccine, two type A strains, PR8 and Weiss, and one type B strain, Lee, were used.

As a control for both the vaccine and the laboratory method, and as a basis of comparison of the results for children with those obtained for adults, a group of medical, dental and nursing students were inoculated, subcutaneously, with the usual adult dose of 1 cc. Two vaccines were used in this group: Vaccine A was the one used for the children, and vaccine B was another commercially available vaccine, which differed from vaccine A in that it was prepared by adsorption on calcium phosphate.

METHODS

Vaccination was carried out in several ways: 1. A single subcutaneous injection of 0.5, 0.25 or 0.125 cc., the dose being determined roughly by age. The children were divided into three groups: those 9 months to 4 years, those 5 to 8 years and those 9 to 14 years of age. The choice of dose for the most part was on the basis of the largest dose for the oldest age group, and so on. However, 3 children in the second age group were given 0.5 cc. 2. Single intradermal injection of

10. This vaccine was provided by Eli Lilly & Company, Indianapolis 6.

0.1 cc. 3. Two intradermal injections of 0.1 cc., given three days apart. The last two methods were used with children of all ages.

All injections were given with 26 gage needles. Subcutaneous injections were given in the deltoid region and intradermal injections on the flexor surface of the forearm, both arms being used when two injections were given. A 5 cc. syringe was used for the subcutaneous injections and a tuberculin syringe for the intradermal injections.

All children who were to receive the vaccine intradermally were tested a day in advance with 0.1 cc. of a 1:100 dilution injected intradermally, the test reaction being read at twenty minutes, two hours and twenty-four hours, using the usual standards of allergy skin tests.

The local reaction to inoculation was observed and recorded at one, four, twenty-four and forty-eight hours after injection. Temperatures were recorded at four hour intervals on all patients for two days before and four days after inoculation.

The serums were tested for influenza antibody by the chicken cell agglutination inhibition method of Hirst[11] with slight modifications.[12] The viruses used for the tests were the PR8 strain of type A influenza, which had been through 352 mouse lung passages and 65 egg passages, and the Lee strain of type B, which had been

TABLE 2.—*Mean Initial and Final Titers, Together with Fold Increase in Titer, to the Two Strains of Influenza Virus in the Adult Group Inoculated with Influenza Vaccines A and B*

		PR8 Strain			Lee Strain		
Group	No. of Persons	Initial Titer	Final Titer	Rise	Initial Titer	Final Titer	Rise
Vaccine A	23	56.02	299.2	5.34	40.25	250.4	6.22
Vaccine B	27	25.96	187.8	7.23	21.87	97.14	4.44
Total	50	36.94	232.6	6.29	28.96	149.5	6.16

through 84 mouse lung passages and 24 egg passages. These strains were provided by Dr. Monroe Eaton, of the State of California Virus Laboratory at Berkeley, Calif. Changes in complement-fixing antibodies[13] were determined on the serums of several patients who showed minimal rises by the agglutination inhibition test after vaccination.

In the tables giving the serologic results, all titers are expressed as the denominator of the initial serum dilution which completely inhibited agglutination of the chicken red blood cells. The mean titer of the groups presented is the geometric mean of the individual titers, and the mean rise is the geometric mean of the individual fold increases in titer. All titers of less than 1:8 were arbitrarily assumed to be 1:4.

RESULTS

The results for the adult group studied are presented in table 2. The mean rises in titer to the two strains of influenza virus were

11. Hirst, G. K.: The Quantitative Determination of Influenza Virus and Antibodies by Means of Red Cell Agglutination, J. Exper. Med. **75**:49-64 (Jan.) 1942.

12. Bodily, H. L., and Eaton, M. D.: Specificity of the Antibody Response of Human Beings to Strains of Influenza Virus, J. Immunol. **45**:193-204 (Nov.) 1942.

13. Eaton, M. D., and Rickard, E. R.: Application of the Complement-Fixation Test to the Study of Epidemic Influenza, Am. J. Hyg., Sect. B **33**:23-35 (Jan.) 1941.

comparable for the two vaccines. The over-all average for the entire group of 50 adults was used in subsequent tables for comparison with the results for the children.

Reactions.—Tables 3 and 4 present the incidence of reactions to the vaccine. A reaction was defined as any sharp rise in rectal temperature to 100 F. or over. In table 3 it can be seen that the majority of reactions occurred within the first twelve hours after inoculation by any route or with any dose. The febrile rises to 101 F. or over were almost entirely confined to the group receiving the subcutaneous injec-

TABLE 3.—*Incidence and Character of the Systemic Reaction to Inoculation by the Three Methods*

Route and Dose	No. of Children with Fever in 12 Hours	No. of Children with Fever in 24 to 36 Hours	No. of Children with Temperatures of 101 F. or Over	Total Number with Fever	No. of Children with Constitutional Symptoms	Incidence of Systemic Reaction, per Cent
Subcutaneous, all doses	13	3	12	16	10	59
Intradermal, 0.1 cc.	5	3	2	8	0	26
Intradermal, 0.1 cc. × 2	5	2	1	7	1	35

TABLE 4.—*Correlation of Age with Incidence of Reaction Following Inoculation by the Two Routes*

Age Group	Subcutaneous: All Doses		Intradermal: Single or Double Doses	
	Total No. of Children	Per Cent with Reaction	Total No. of Children	Per Cent with Reaction
9 mo. to 4 yr.	7	57	24	33
5 to 8 yr.	6	50	16	12
9 to 14 yr.	14	57	12	40

tion. Furthermore, in this group the reactions were usually accompained by symptoms such as headache and vomiting or with complaint by the older children of "feeling sick." In the groups receiving intradermal inoculations, such complaints were conspicuously absent. The over-all incidence of reaction in these two groups was slightly more than one-half that in the group receiving subcutaneous injection. It should be noted that when a child reacted to the first of two intradermal inoculations he reacted comparably to the second.

In table 4 the incidence of reaction for the three age groups is presented. In the group given subcutaneous inoculations the rate was about the same for children of all age groups, while in the group given intradermal inoculations the children aged 5 to 8 years showed a remarkably lower rate.

All the children receiving vaccine intradermally were tested with 0.1 cc. of a 1:100 dilution of vaccine. These tests gave negative reactions in every instance. In all intradermal inoculations with undiluted vaccine, a sharp, "stinging" pain at the site of injection occurred one to two minutes after the needle had been withdrawn. The younger child occasionally cried at this moment, and the older ones complained or suddenly began to rub the area. This pain lasted about five minutes and was presumed to be due to the formaldehyde content of the vaccine.

The local reaction to 0.1 cc. of the undiluted vaccine given intradermally was uniform in all children. It reached maximum intensity in twenty-four to thirty-six hours, at which time an area of redness about 2 cm. in diameter was present, with an area of induration extending out approximately another centimeter. No pseudopod forma-

TABLE 5.—*Correlation of Dose and Route with Mean Initial and Final Titers and Mean Fold Increase in Titer to the Two Strains of Influenza*

Dose, Cc.	Route	No. of Subjects	PR8 Strain			Lee Strain		
			Initial Titer	Final Titer	Rise	Initial Titer	Final Titer	Rise
1.0	Subcutaneous	50*	36.94	232.6	6.29	28.95	149.5	6.16
0.5	Subcutaneous	10	32.0	433.0	13.5	9.85	149.5	15.2
0.25	Subcutaneous	6	40.3	322.6	8.0	7.12	193.65	27.1
0.125	Subcutaneous	11	9.41	68.9	7.3	5.02	50.23	10.03
0.1	Intradermal	30	10.6	87.4	8.25	7.6	43.7	5.72
0.1, × 2	Intradermal	22	13.92	188.8	13.56	9.64	183.8	19.07

* Adult group of 50 persons included for comparison with the children.

tion or wheals were noted. There was pain on pressure over this area in all children. At forty-eight hours the redness and pain had subsided, but about one-half the children still had palpable induration which lasted another twenty-four to thirty-six hours.

All subcutaneous inoculations were followed by local reactions of pain and induration, resulting in some limitation of motion of the arm in about one third of the children so inoculated. No redness or swelling of the arm was noted, nor was there any palpable involvement of the axillary lymph nodes.

Serologic Results.—In table 5 are presented the serologic results for all groups of children, with those for the adult group for comparison. The highest mean rises in titer to both strains occurred in the groups receiving 0.5 cc. subcutaneously and a total dose of 0.2 cc. intradermally. The highest mean final titer to the PR8 strain was in the group receiving 0.5 cc. subcutaneously, and the highest mean final titer to Lee strain was in the group given 0.25 cc. subcutaneously, while that in the group receiving 0.2 cc. intradermally was probably

not significantly different. The groups showing the lowest rises in antibody to both strains were those receiving 0.125 cc. subcutaneously and the single intradermal injection of 0.1 cc. However, with respect to mean rises, neither of these groups differed significantly from the adult group. The most consistent groups, when high mean rises to both strains are considered, were the group receiving 0.1 cc. in two inoculations three days apart and the group receiving 0.5 cc. subcutaneously.

In table 6 the mean initial and final titers to the two strains, together with the mean rises, are grouped according to range in age, as well as route and dose. The mean initial titer to the PR8 strain, of type A, can be seen to show a definite increase with increasing

TABLE 6.—*Correlation of Age with Mean Initial and Final Titers and Mean Fold Increase in Titer Group*

Age Group	PR8 Strain			Lee Strain		
	Initial Titer	Final Titer	Rise	Initial Titer	Final Titer	Rise
Subcutaneous: All Doses						
9 mo. to 4 yr.	5.94	53.39	8.98	4.41	27.91	6.32
5 to 8 yr.	21.5	350.9	7.47	6.05	116.3	19.22
9 to 14 yr.	37.12	391.6	10.55	9.28	186.3	20.08
Intradermal 0.1 Cc.						
9 mo. to 4 yr.	4.81	46.16	9.59	6.88	37.76	5.48
5 to 8 yr.	9.03	94.7	8.26	5.87	37.3	6.35
9 to 14 yr.	96.8	264.0	2.78	10.0	80.63	8.63
Intradermal: 0.2 Cc. × 2						
9 mo. to 4 yr.	4.52	54.85	12.14	5.27	128.0	24.28
5 to 8 yr.	17.66	350.5	19.84	10.01	231.8	23.16
9 to 14 yr.	57.02	443.4	7.77	20.56	203.2	9.88
All Routes and Doses						
Under 7 yr.	6.36	59.94	9.4	6.15	56.37	9.16
Over 7 yr.	41.85	531.3	12.74	11.45	152.5	13.32

age in all the groups of patients studied. The difference was even more striking when the groups of children were divided into those under and those over 7 years of age. The mean initial titers to the Lee strain, representing type B influenza, showed less variability among the groups of children. However, in all groups the titer tended to increase slightly with age. This tendency was less pronounced for the Lee strain than for the PR8 strain. The final titers to both strains reached by the youngest age group were low compared with those of the older age groups. This difference is emphasized by the division of the children at 7 years of age, reflecting in part the lower initial titers in the children under 7 years.

The mean rise to the PR8 strain following subcutaneous inoculation showed a tendency to remain constant with changes in the age group. In the intradermal inoculation groups this rise tended to be less in the children of the oldest age group.

In both the group receiving subcutaneous and that receiving intradermal inoculation the mean rise to the Lee strain tended to increase with age. However, the group receiving two inoculations intradermally completely reversed this tendency. These changes are summarized in the arbitrary division of the children into two groups: those under 7 years of age and those 7 years of age and over. It can be seen that the children in the younger age group had a slightly lower mean rise to each strain than those in the group over 7 years of age.

TABLE 7.—*Numerical Distribution of Children According to Magnitude of Increase in Titer Correlated with Dose and Route*

Dose, Cc.	Route	No. of Children	Fold Increase				Total with 0 to 6 Fold Increase	Total with 8 to 512 Fold Increase
			0 to 6	8 to 12	16 to 48	64 to 512		
			PR8 Strain					
0.5	Subcutaneous	10	0	5	5	0	0	10
0.25	Subcutaneous	6	2	1	3	0	2	4
0.125	Subcutaneous	11	5	1	5	0	5	6
0.1	Intradermal	30	13	6	8	3	13	17
0.1, × 2	Intradermal	22	7	4	8	3	7	15
			Lee Strain					
0.5	Subcutaneous	10	3	1	3	3	3	7
0.25	Subcutaneous	6	0	1	3	2	0	6
0.125	Subcutaneous	11	3	5	2	1	3	8
0.1	Intradermal	30	16	7	7	0	16	14
0.1, × 2	Intradermal	22	1	7	13	1	1	21

TABLE 8.—*Numerical Distribution of Children with Minimal Increase in Titer, Correlated with Dose and Route*

Dose, Cc.	Route	Total Number in Group	At Least 8 Fold to PR8 Strain But Not to Lee Strain	At Least 8 Fold to Lee Strain But Not to PR8 Strain	Less Than 8 Fold to Both Strains	No Response to Either Strain
0.5	Subcutaneous	10	3	0	0	0
0.25	Subcutaneous	6	0	2	0	0
0.125	Subcutaneous	11	1	3	2	0
0.1	Intradermal	30	8	5	8	2
0.1, × 2	Intradermal	22	0	6	1	0

The distribution of the various magnitudes of increase in antibody to the two strains resulting from the various methods is presented in table 7. The most striking observation is that after the two intradermal inoculations a considerably larger proportion of increases fell in the 8 to 512 fold range than after the single intradermal inoculation.

In table 8 data on the children with minimal or no increase in antibodies to the two strains are presented. The 0.125 cc. dose given subcutaneously and the single dose intradermally most frequently failed to produce an increase of eight fold or more to either strain. The

single intradermal dose in 2 children also resulted in no increase whatever to either strain. Complement-fixing antibody was determined on a number of these pairs of serums which had showed minimal or no rise by the agglutination inhibition titration. One of 9 children who had shown no increase to either strain by the agglutination inhibition method showed an eightfold rise to the PR8 strain and a sixty-four fold rise to the Lee strain by complement fixation. The remaining children showed no rise in complement-fixing antibody.

In table 9 the increase in antibody of children with low initial titers is compared with that of children showing higher initial titers. It can be seen that in the groups receiving vaccine intradermally the children with initial titers of 1:8 or less responded with greater increases to both strains but that this tendency was not observed for the group receiving subcutaneous inoculation.

TABLE 9.—*Mean Fold Increase in Titer to the Two Strains of Influenza Virus Correlated with the Magnitude of the Initial Titer to That Strain and with Route of Inoculation*

		Initial Titer 8 or Less		Initial Titer Greater Than 8	
Dose, Cc.	Route	PR8 Strain	Lee Strain	PR8 Strain	Lee Strain
All doses	Subcutaneous	6.5	14.4	11.35	14.61
0.1	Intradermal	10.24	6.18	3.98	4.86
0.1 × 2	Intradermal	27.88	21.35	6.61	10.65

Sampling of all groups of children four to six weeks after vaccination showed no further increase or any significant decrease in antibody as compared with the results obtained at twelve to sixteen days after vaccination.

COMMENT

The incidence of reaction to the subcutaneously administered vaccine in the present investigation compares with the results reported by Grant.[4] The children receiving vaccine subcutaneously commonly had symptoms other than fever, resulting in comment by both the nurses and the older children. Two of the younger children in this group were sick enough to cause the nurses to call the intern. The most striking observation, however, was that reactions following intradermal inoculation were both less frequent and less severe. The children inoculated intradermally were known to have had a reaction only on examination of the temperature records. These results are in harmony with the conclusions drawn by investigators who used other immunizing agents intradermally [14] and also with the results reported for adults after intradermal administration of influenza vaccine.[8]

14. Tuft.[5] Robinson.[6] Kern and others.[7]

The more generalized type of reaction, such as followed the subcutaneous inoculations in the present investigation, has been explained as a reaction to the injection of a foreign protein.[9] While this explanation may well apply to some or all of such reactions, it is possible also to ascribe the reaction to the virus or to products of the virus in the vaccine. Henle and Henle [15] produced evidence that the influenza viruses have toxic properties. These properties may on subsequent investigation be shown to bear a relation to both the generalized and the local reactions to the virus. Salk,[16] in discussing a reported fatal reaction to influenza virus vaccine in a child,[17] stressed the lack of evidence for an allergic basis and also pointed out that the constitutional reactions noted in adults after inoculation with the vaccine seem to be proportional, not only in frequency but also in severity, to the concentration of virus injected. While it is not the intention of this discussion to minimize the dangers of sensitivity to egg protein in the use of vaccines prepared from eggs, it should, nevertheless, be realized that factors in the vaccine other than the egg protein may explain some of the general or local reactions.

The local reaction to the vaccine administered intradermally is, in the opinion of several investigators, of some significance. Beveridge and Burnet [18] studied the local reaction of both adults and children to intradermally injected, boiled allantoic fluid which had been infected with either of two strains of influenza virus, or with the virus of Newcastle disease of chickens. Assuming mutual control by these three viruses, they concluded that the degree of reaction locally paralleled the serologic titer of antibody in children to that virus, and they suggested that the reaction was based on sensitivity to the virus strain, and hence to past infection with that strain. In the present investigation, all children reacted to the undiluted vaccine given intradermally. Furthermore, the results of the test with a dilution of 1:100 had no correlation with the reaction to the undiluted vaccine. Comparison of these results with those of the aforementioned authors may not be possible, however, because of the differences in the injected materials.

Few studies have been made on the levels of antibody to strains of influenza in the younger age groups. The prevaccination titers in the present investigation represent additional information on this point.

15. Henle, G., and Henle, W.: Studies on the Toxicity of Influenza Viruses: I. Effect of Intracerebral Injection of Influenza Viruses, J. Exper. Med. **84**:623-637 (Dec.) 1946.

16. Salk, J. E.: Reactions to Influenza Virus Vaccines, Correspondence, J. A. M. A. **134**:393 (May 24) 1947.

17. Curphey, T. J.: Fatal Allergic Reaction Due to Influenza Vaccine, J. A. M. A. **133**:1062-1064 (April 12) 1947.

18. Beveridge, W. I. B., and Burnet, F. M.: A Cutaneous Reaction to the Influenza Viruses, M. J. Australia **1**:85-89 (Jan. 29) 1944.

Francis and Magill in 1936 [19] showed that after the first year of life one half of all the persons studied possessed neutralizing antibody to the PR8 strain in their serums. They stated that it could be assumed that without infection there would be no neutralizing antibody to a given strain of influenza virus. Rickard and Horsfall [20] followed the level of neutralizing antibody in the serums of 72 infants from birth to over 1 year of age and observed that during the first two months the levels were almost identical with those of the mothers. After that time the level dropped rapidly, so that at 1 year of age virtually no infant possessed any neutralizing antibody. Adams and co-workers,[21] in studying an epidemic of influenza type A in infants and children, observed lower titers with the agglutination-inhibition titers in children under 23 months of age than in those over that age.

A close mathematical correlation between neutralizing and agglutination inhibition antibodies has been demonstrated.[11] However, it has been shown that in the low titers of the latter antibodies there may be nonspecific inhibition of the agglutination of chicken cells.[11] While this nonspecific inhibition cannot be eliminated entirely, we believe that the present series of titers can be safely correlated with age and compared with the previously reported results. For statistical purposes in the present report, all titers of less than 1 : 8 were considered to be 1 : 4. From table 6 it can be seen that the present data show essentially no significant titers to PR8 the strain in children under 4 years of age and a steady increase in the mean titer after that time. The initial titers to the Lee strain, representing type B influenza, also were low in children under 4 years of age and remained at a considerably lower level in most of the groups studied. The investigation of the possible relation of these data to the past incidence of these types of influenza would require a much larger series of subjects than the present one.

The mean rises to the two strains of influenza accomplished by the various combinations of routes and doses in the present series of children are comparable in a general way to the reported results following administration of 1 cc. subcutaneously in adults,[2] and they are also not greatly different from the results found by another group of

19. Francis, T., Jr., and Magill, T. P.: The Incidence of Neutralizing Antibodies for Human Influenza Virus in the Serum of Human Individuals of Different Ages, J. Exper. Med. **63**:655-668 (May) 1936.

20. Rickard, E. R., and Horsfall, F. L., Jr.: The Relationship Between Neutralizing Antibodies Against Influenza A Virus in the Sera of Mothers and Infants, J. Immunol. **42**:267-272 (Nov.) 1941.

21. Adams, J. M.; Thigpen, M. P., and Rickard, E. R.: An Epidemic of Influenza A in Infants and Children, J. A. M. A. **125**:473-476 (June 17) 1944.

investigators,[8] using the intradermal route in adults. It should be pointed out that differences in serologic technic make strict comparison with the latter results impossible. The fold increase in antibody to type A and type B influenza in children following administration of 0.5, 0.25 and 0.125 cc. subcutaneously and 0.1 cc. intradermally was equal to, or slightly better than, the results in adults, while the response to 0.1 cc. given intradermally twice was almost double the usual response in adults. The last method seemed most satisfactory when compared with the other routes and doses. The difference between the mean rise to the two strains in the younger and that in the older age group does not seem to be of great statistical importance. Adams and co-workers [21] showed no difference in the serologic response to infection with type A influenza among various age groups.

It has been demonstrated that the level of antibody is correlated with resistance or susceptibility to infection with a homologous strain.[22] If, from this correlation, it can be assumed that subjects with high titers have greater resistance, then in the present investigation the best results were obtained in older children and by the subcutaneous and the two dose–intradermal methods. It is important, however, to stress that no information correlating the incidence of clinical influenza in children with serologic antibody titers is available, and it is therefore unwarranted to conclude that any of the final titers produced in these children afforded adequate or inadequate protection.

The children who showed minimal or no response to either or both strains of the vaccine represent an unsolved problem at present. Determinations of complement-fixing antibody did not throw light on this problem. It is interesting that all but 2 of these children showed fever and general reaction to the subcutaneous inoculation or the expected local reaction to the intradermal inoculation.

The problem of the strain-specificity of the response to infection and to vaccination has received a great deal of attention in the literature. Certain aspects of this problem apply to the vaccination of children. Burnet,[23] in 1937, postulated that the antibody response to infection in

22. Stokes, J., Jr., and Henle, W.: Studies on Methods of Prevention of Epidemic Influenza, J. A. M. A. **120**:16-20 (Sept. 5) 1942. Henle, W.; Henle, G., and Stokes, J., Jr.: Demonstration of the Efficacy of Vaccination Against Influenza Type A by Experimental Infection of Human Beings, J. Immunol. **46**: 163-175 (March) 1943. Francis, T., Jr.; Salk, J. E.; Pearson, H. E., and Brown, P. N.: Protective Effect of Vaccination Against Induced Influenza A, Proc. Soc. Exper. Biol. & Med. **55**:104-105 (Feb.) 1944. Salk, J. E.; Pearson, H. E.; Brown, P. N., and Francis, T., Jr.: Protective Effect of Vaccination Against Induced Influenza B, ibid. **55**:106-107 (Feb.) 1944.

23. Burnet, F. M.: Influenza Virus in the Developing Egg: V. Differentiation of Two Antigenic Types of Human Influenza Virus, Australian J. Exper. Biol. & M. Sc. **15**:369-374 (Dec.) 1937.

children might be found to be as sharply strain distinct as in the ferret. Smith and Andrewes [24] showed that the efficacy of active immunization against heterologous strains in experimental animals depended on antigenic relations and that in ferrets with no previous influenza infection the response was most strain specific. Taylor and co-workers [25] demonstrated both experimentally in animals and epidemiologically in human subjects that strain differences in the response to immunization and infection were most manifest when the antibody titer was of a low order and that most human subjects with previous influenzal infection will respond to another infection with a more heterologous group of antibodies. Burnet and Stone [26] observed that children and adolescents convalescent from type B influenza commonly had the highest titers against the specific strain involved in the infection. The implication of these findings in regard to the value of vaccination against influenza is obvious, and it remains for further investigation to show how broad may be the antibody base following the use of the presently available combined influenza vaccines. This work is in progress and will be made the basis of a subsequent report.

SUMMARY AND CONCLUSIONS

Seventy-nine children were inoculated subcutaneously or intradermally with combined type A and type B influenza virus vaccine.

Febrile reactions, with temperatures usually over 101 F., and, commonly, malaise and headache and, occasionally, vomiting, occurred in more than one-half the children receiving vaccine subcutaneously.

The reactions following intradermal inoculation with either 0.1 cc. in one dose or 0.2 cc. in two doses were approximately one half as frequent as those following subcutaneous inoculation and were not accompanied with either high temperatures or constitutional symptoms.

The serologic response to vaccination with influenza virus vaccine was comparable in all groups to the results for adults. The two doses of 0.1 cc. given three days apart produced the most satisfactory results.

The prevaccination titers to type A influenza in these children were approximately in proportion to age.

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24. Smith, W., and Andrewes, C. H.: Serological Races of Influenza Virus, Brit. J. Exper. Path. **19**:293-314 (Oct.) 1938.

25. Taylor, R. M.; Dreguss, M., and de Ritis, F.: Antigenic Behavior of Certain Hungarian Strains of Epidemic Influenza Virus, Am. J. Hyg., Sect. B. **31**:36-45 (Jan.) 1940. Taylor, R. M., and Dreguss, M.: Influenza Virus Studies During the 1939 Epidemic in Central Europe, J. Infect. Dis. **68**:79-89 (Jan.-Feb.) 1941.

26. Burnet, F. M., and Stone, J. D.: Serological Response to Influenza B Infection in Human Beings: Differentiation of Specific and Nonspecific Type Reactions, Australian J. Exper. Biol. & M. Sc. **24**:207-212 (Sept.) 1946.

The theoretic limitations to the protection afforded by high antibody levels in children against the strains of influenza virus available at present are discussed.

The data presented support the conclusion that the intradermal route of inoculation in children, especially when two doses of 0.1 cc. each are given three days apart, produces increases in antibody, comparable to those in adults and is accompanied with greatly lowered incidence and severity of reactions as compared with the subcutaneous route.

Miss Mirra Scaparone, B. A., gave technical assistance in this study.

Pamassus and Third Avenues (22).

ESSENTIAL XANTHOMATOSIS

Fifteen Years' Observation on a Case Occurring in a Family with Hypercholesteremia

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AND
WARREN M. SPERRY, Ph.D.
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IN 1936 we[1] recorded the results of a year's study (April 1934 to May 1935) on H. R., a boy who when first seen by one of us (B. S.) in 1932 was 9 years of age, and who, when admitted in April 1934 to the pediatric service of Mount Sinai Hospital, New York, presented a picture of severe xanthoma tuberosum with pronounced hypercholesteremia. The present report describes the subsequent course of the disease and provides further observations on the patient and his family. We wish to stress particularly two features which we believe unique: (1) The patient lived thirteen years on a diet virtually free of cholesterol with little, if any, change in his condition, and (2) the father, mother and 1 brother were hypercholesteremic, with no evidence of xanthomatosis. The heredofamilial considerations raised by the latter observation are discussed in considerable detail.

REPORT OF A CASE

History.—The patient's history is irrelevant except for features concerned with his present illness; these are reviewed briefly. When he was 3 years of age, it was noted that the blood serum was hyperlipemic; and cream, which had been given in liberal quantities, was removed from the diet for several weeks. When he was 4 years old, about half a dozen xanthomatous areas, each approximately 0.5 cm. in diameter, were observed in the deltoid region of the left arm. Despite treatment by a dermatologist, similar areas appeared in the deltoid region of the right arm and on both elbows, the hip, the knees and the back. Roentgen therapy, local implantation of radon seeds and a spray of carbon dioxide snow had no definite effect.

The appearance and the extent of the lesions as they existed in 1934 were shown in the photographs included in our first paper. The tumors on the knees and elbows were similar in their localization to the lesions of psoriasis. Particularly interesting were the tumors in the gluteal region, the large pendulous tumors about the achilles tendons and the tumors on the knuckles of the fingers. Outstanding features were the pronounced arcus "senilis" corneae and the small xanthelasma palpebrarum,

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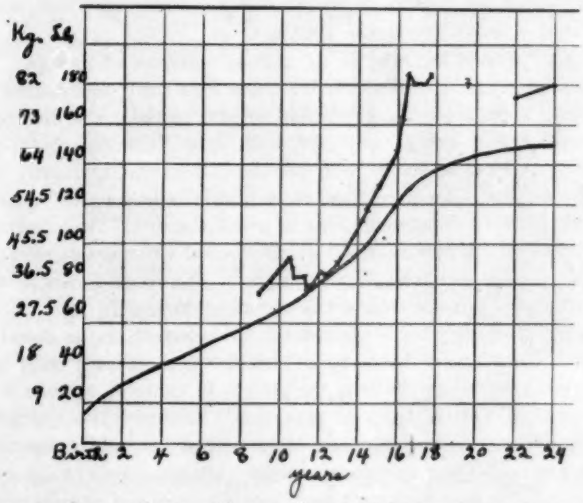
From the Children's Department, Mount Sinai Hospital, and the Department of Biochemistry, New York State Psychiatric Institute.

1. Sperry, W. M., and Schick, B.: Essential Xanthomatosis: Treatment with Cholesterol-Free Diet in Two Cases, Am. J. Dis. Child. **51**:1372 (June) 1936.

lesions which are more characteristic of the advanced forms of essential xanthomatosis in adults. It may be said at this point that little change has been noted since 1935. However, we have the impression that, on the whole, with advancing years the tumors slowly have become less elevated and less intensely yellow. These changes have seemed more pronounced during the past four years. The patient went through normal sexual development, and this revolution in the endocrine orchestra may, in some way, have effected the arrest of the disease.

The hypercholesteremia, which was an outstanding feature, will be discussed later.

The patient's growth in respect to his increase in height was normal. He stopped growing about six years ago. The curve for weight (chart) is somewhat irregular. The weight was above normal when the patient was first seen, but it was reduced with thyroid treatment and dietetic measures and remained about normal until he was 14 years of age. Since that time the patient has been overweight, a reflection of his excellent appetite despite the monotony of the vegetable diet on which he lived.



Weight curve for patient with xanthoma tuberosum accompanying hypercholesteremia.

Treatment.—Thyroid, insulin, lipocaic, the vitamin B complex, ultraviolet radiation and a cholesterol-free diet were all tried as therapeutic measures. Thyroid, which was given over several extended periods because the metabolic rate was low, had some influence on the weight and the metabolic rate, but none on the lesions or the hypercholesteremia.

After reading an enthusiastic article [2] on the favorable effect of insulin on essential xanthomatosis, we administered it at the rate of 10 U.S.P. units twice daily, and we also somewhat restricted the carbohydrate intake from March 1936 to December 1937. During this period the cutaneous manifestations showed no change, but an apparent decrease took place in the cholesterol concentration of the blood serum; it fell from 826 mg., in April 1936, to 689 mg. per hundred cubic centimeters in December 1937.

2. Brodin, P., and Chauffard, A.: Insulin Treatment of Diabetic Xanthoma, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:1003 (June 18) 1926.

From January 1939 to May 1939 lipocaic was administered at the rate of 7 to 10 capsules (each containing 0.5 Gm.) per day. No definitely favorable effect on the lesions or on the hypercholesteremia was noted; indeed, the cholesterol concentration of the blood serum appeared to rise from 730 to 814 mg. per hundred cubic centimeters during the period. Rosenak [3] also observed no effect of lipocaic in a patient with xanthoma tuberosum, but Dragstedt and associates [4] reported excellent results with more intensive therapy.

Vitamin B complex was given without any decisive effect on the disease.

The insulin, lipocaic and vitamin B complex increased the already good appetite of the patient and were responsible to some degree for the increase in weight referred to previously. With lipocaic there was a gain of 5 Kg. in a few weeks.

Treatment with ultraviolet radiation, though of many months' duration, had no effect.

Both the patient and his mother expressed the opinion that with each of the aforementioned treatments there was some improvement in the cutaneous manifestations; to them the lesions seemed less elevated and somewhat lighter in color, and in certain areas the centers of the lesions appeared more normal. However, objectively, little if any change was apparent.

The principal interest centered in the diet as a means of therapy. The patient had eaten no foods rich in cholesterol for some time prior to his admission to the hospital in 1934. Soon after his admission he was placed on a diet containing no foods of animal origin except skimmed milk. He followed this regimen until February 1947. It must be pointed out that the patient was extremely conscientious in adhering to the diet. He obeyed the rules faithfully in spite of repeated attempts of friends and relatives to persuade him to break the diet. We are convinced that for thirteen years this patient received no cholesterol whatever of exogenous origin, except possibly for traces in the skimmed milk. The result has been disappointing save in one respect: No new lesion has appeared during the long period of treatment. As noted previously, it is possible that this arrest of the disease was spontaneous; but it seemed more likely to us that the diet deserved most of the credit, and we have felt justified in advising the patient to continue it, even though it was difficult to maintain. During the year previous to February 1947 the patient became very unhappy and depressed because of his meatless diet, and a mental breakdown appeared imminent. Since a breakdown might have more serious consequences than a recrudescence of the xanthomatosis, and since we could not be sure that the cholesterol-free diet was responsible for the arrest of the disease, the patient was advised in February 1947 to include lean meat three times a week in his diet. Examinations two months, seven months and twenty-two months later revealed no effect of this change in the patient's physical status or on the hypercholesteremia, but his mental outlook was much improved. It will require a long period of observation to determine whether the ingestion of meat has any effect on the xanthomatosis.

Surgical treatment was contraindicated from the large number and the widespread distribution of the tumors, but the disfiguration of the patient's hands led

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3. Rosenak, B. D.: A Case of Xanthoma Tuberosum Treated with Lipocaic, Ann. Int. Med. **19**:514 (Sept.) 1943.

4. (*a*) Dragstedt, L. R.: Personal communication to the author. Of 6 patients with the various types of xanthomatosis, 4 showed distinct decrease in blood cholesterol after treatment, the levels in 3 finally becoming normal. The xanthomatous nodules in the skin improved. (*b*) Stewart, C. D.; Clark, D. E.; Dragstedt, L. R., and Becher, S. W.: The Experimental Use of Lipocaic in Treatment of Psoriasis, J. Invest. Dermat. **2**:219 (Aug.) 1939.

to the decision to remove two particularly ugly tumors from the right hand on Dec. 27, 1939. The results of an analysis of the biopsy material are given in table 1. They may be compared with other determinations of lipids in xanthomas in a review by Sperry [5] (his table 3). Carotene was present and was probably responsible for the yellow color of the lesions. The presence of carotene may be an indication of a disturbance in vitamin A metabolism, possibly a difficulty in converting the provitamin, carotene, into vitamin A, but the patient had no clinical signs of vitamin A deficiency.

COMMENT

Hypercholesteremia.—During the year covered by our previous report,[1] the total cholesterol content of the blood serum varied within the limits of 685 and 955 mg. per hundred cubic centimeters, with the large majority of values above 800 mg. Since then, cholesterol has been measured on fifteen occasions by the method of Schönheimer and Sperry,[6] or a modification thereof.[7] The results (table 2) show a continued pronounced hypercholesteremia in every instance, but there appears to have been a tendency toward a decrease in the cholesterol

TABLE 1.—*Analysis of Biopsy Material*

Constituent	Percentage in Tissue: Calculated on Wet Weight	Percentage in Tissue: Calculated on Dry Weight
Water	65.7	....
Total lipid (petroleum ether soluble)	11.5	33.7
Total cholesterol *	5.0	14.5
Free cholesterol	1.2	3.4
Combined cholesterol	3.8	11.1

* Ratio of combined to free cholesterol: 3.2.

concentration of the blood serum: Most of the values were below 800 mg. per hundred cubic centimeters, and since 1942 they have remained below 700 mg. Unfortunately, in view of the considerable variability in the cholesterol level in this patient shown during the period in 1934, when measurements were made every three days (table 3 of the previous paper), we cannot be certain that a real decrease has taken place. It is possible that in the widely separated determinations we were able to carry out during these years we chanced to encounter low values, such as that for April 24, 1934. (It may be stated at this point that because of this variability we attached no significance to the apparent changes following administration of insulin and lipocaic which were noted previ-

5. Sperry, W. M.: The Biochemistry of the Lipoidoses, J. Mt. Sinai Hosp. **9**:799 (Nov.-Dec.) 1942.

6. Schönheimer, R., and Sperry, W. M.: A Micromethod for the Determination of Free and Combined Cholesterol, J. Biol. Chem. **106**:745 (Sept.) 1934.

7. Sperry, W. M.: The Schoenheimer-Sperry Method for the Determination of Cholesterol, New York, New York State Psychiatric Institute and Hospital, April 1945.

ously.) However, despite this uncertainty, the most reasonable interpretation of the data is that some decrease in the cholesterol level occurred under the influence of the cholesterol-free diet. Whether this interpretation is accepted or not, the remarkable fact is that a pronounced hypercholesteremia was maintained despite the virtual absence of cholesterol from the diet for thirteen years.

TABLE 2.—*Cholesterol and Lipid Phosphorus Contents of Blood Serum of H. R. and of His Parents and Brothers*

Subject	Date	Cholesterol, Mg./100 Cc.			Ratio of Combined Cholesterol to Free Cholesterol	Lipid Phosphorus, Mg./100 Cc.
		Total	Free	Combined		
H. R.	4/10/36	826	208	618	2.97	....
	11/16/36	708	199	509	2.56	....
	12/17/37	689	195	494	2.53	....
	12/28/38	730	233	497	2.13	....
	3/ 3/39	689	200	489	2.45	....
	5/19/39	814	228	586	2.57	....
	12/27/39	689	211	478	2.27	....
	4/16/41	800	220	580	2.64	....
	4/14/42	646	173	473	2.73	....
	1/28/47	666	201	465	2.31	20.3
	4/25/47	647	201	446	2.22	19.8
	9/10/47	638	188	450	2.39	15.2
	3/ 9/48	743	202	541	2.69	19.2
	6/25/48	652	181	471	2.60	18.6
	7/15/48	659	176	483	2.74	....
Mother	11/16/36	444	117	327	2.79	....
	12/17/37	386	110	276	2.52	....
	12/28/38	528	156	372	2.38	....
	4/17/41	460	124	336	2.71	....
	4/ 7/42	502	146	356	2.44	....
	1/30/47	437	128	309	2.41	16.6
	6/25/48	514	145	369	2.54	16.7
Father	3/ 8/47	449	130	319	2.45	14.0
D. R. (brother)	2/ 4/37	477	122	355	2.91	....
	12/17/37	376	98	278	2.84	....
	12/28/38	381	113	268	2.37	....
	4/17/41	438	111	327	2.95	....
	4/ 7/42	576	147	429	2.92	....
	2/ 8/47	455	135	320	2.37	15.5
H. R. (brother)	2/ 4/37	364	95	269	2.83	....
	12/17/37	278	70	208	2.97	....
	12/28/38	294	86	208	2.42	....
	4/17/41	353	90	263	2.92	....
	4/ 7/42	344	98	246	2.51	....
	2/ 8/47	281	86	195	2.27	12.5

It should be stressed that, with the possible exception of two determinations in which slightly lower values were obtained, the ratio of combined to free cholesterol remained within the normal range of variation throughout the period of study. The significance of this proportion was discussed in detail in our previous publication.[1]

Heredofamilial Aspects.—In our first communication, we reported the finding of hypercholesteremia in the patient's mother, father and 1 brother (D. R,). The cholesterol level for another brother (H. R.), who was 5 years of age at the time, was normal. Since then, several determinations for the mother and the 2 brothers have been carried out.

and recently the father's cholesterol level was measured again. The results (table 2) show a continued hypercholesteremia in the mother, and the single analysis of the father's serum gave a value similar to that obtained thirteen years before. Had it been possible to obtain a series of determinations on the father, as on the mother, the picture probably would have been the same. Brother D. R. maintained his hypercholesteremia, and the level for brother H. R. increased notably over the low normal concentration which he showed at the age of 5 years.

The values for brother H. R. well illustrate the difficulty in interpreting the significance of total cholesterol concentrations in the blood serum. All values for H. R. were within the range found by Sperry [8] in healthy persons with the same method. Indeed, since H. R. is in excellent health, the concentrations of cholesterol in his serum, as reported in table 2, could be included in the series of "normal" values if they had been obtained without knowledge of his family background or of his low concentration at an early age. Actually, they are "normal" for brother H. R., and we might go further and suggest that the still higher and definitely hypercholesteremic values for the other members of the family are the "normal" concentrations for those persons, as determined by their hereditary background. The word "normal" has doubtful significance when applied to the cholesterol concentration of the blood serum. As pointed out by Sperry,[8] persons with cholesterol concentrations in the upper part of the normal range may be abnormal in the sense that they have a latent tendency to the development of xanthomatosis, a tendency which is probably present in the case of H. R.

None of the members of the family except the patient showed any clinical symptoms pointing to xanthomatosis; the parents had no xanthelasma palpebrarum; they would all be considered in good health. The only indication of any abnormality is a tendency toward bad complexion in the mother. On an unrestricted diet a somewhat darker color develops in the skin, and it becomes rough. These symptoms improve on a diet low in cholesterol.

The findings in this family emphasize the heredofamilial nature of essential xanthomatosis of the xanthoma tuberosum type and add support to the hypothesis advanced by Schmidt [9] that hypercholesteremia is the primary disturbance in this disease. The tendency of xanthoma tuberosum to occur in several members of a family has been known for a long time; many families tainted with the disease have been described, and the presence of hypercholesteremia without manifestations of xanthomatosis in members of such families has been reported by several

8. Sperry, W. M.: The Relationship Between Total and Free Cholesterol in Human Blood Serum, J. Biol. Chem. **114**:125 (May) 1936.

9. Schmidt, E.: Beiträge zur Xanthomfrage, Arch. f. Dermat. u. Syph. **104**:408, 1922.

authors. Bloom, Kaufman and Stevens [10] reviewed this literature and added an interesting example of their own. The parents of 13 children were second cousins, and the cholesterol concentration of the father's serum was 315 mg. per hundred cubic centimeters. Of 9 siblings who survived infancy, 5 had severe xanthoma tuberosum. Cholesterol levels were measured in 4 of the children, and values of 266, 285, 333 and 730 mg. per hundred cubic centimeters, respectively, were obtained. Cholesterol concentration was also measured in 3 of the 4 siblings without the disease. In 1 child the concentration was below 230 mg. (taken as the upper limit of normal with the method used), and in the others it was 280 and 355 mg. per hundred cubic centimeters, respectively. All these values, with the exception noted, were considered by Bloom and associates to be above normal, but it will be seen that the value for only 1 child is outside the range found by Sperry [8] in healthy persons.

Svendsen [11] reported the most elaborate study of this sort in a single family on record. The cholesterol concentration of the blood serum was determined in the husband, father, 7 siblings and 5 of their consorts, 2 children and 17 nieces and nephews of a woman with xanthomatosis and definite hypercholesteremia (600 mg. per hundred cubic centimeters). None of the relatives had xanthomatosis, but in 12 of them the cholesterol level was considered abnormally high (above 240 mg. per hundred cubic centimeters). All these values (the maximum was 348 mg. per hundred cubic centimeters) are within the range found by Sperry [8] in healthy persons, but the number (5) of them above 300 mg. is higher than would be expected from Sperry's results for an equal number of persons selected at random.

Kornerup [12] observed that the average concentrations of cholesterol and of phospholipids in the blood serum were above normal in 45 subjects with xanthelasma and also in 25 adult members of families subject to that anomaly. In 1 of the latter group the concentration of cholesterol was between 400 and 450 mg. per hundred cubic centimeters.

To our knowledge, the only other report of unquestionable hypercholesteremia in a healthy member of a xanthomatous family was that of Lane and Goodman.[13] The father and a 7 year old daughter had

10. Bloom, D.; Kaufman, S. R., and Stevens, R. A.: Hereditary Xanthomatosis: Familial Incidence of Xanthoma Tuberosum Associated with Hypercholesteremia and Cardiovascular Involvement, with Report of Several Cases of Sudden Death, Arch. Dermat. & Syph. **45**:1 (Jan.) 1942.

11. Svendsen, M.: Are Supernormal Cholesterol-Values in Serum Caused by a Dominantly Inherited Factor? Report of a Family Investigation of Thirty-Four Individuals, Acta med. Scandinav. **104**:235, 1940.

12. Kornerup, V.: Om serums indhold af cholesterol, totalfedt og lipoidfosfor hos normale og hos familier med xanthelasmata, Nord. med **16**:3300 (Dec.) 1942.

13. Lane, G. C., and Goodman, J., Jr.: Xanthoma Tuberosum, Arch. Dermat. & Syph. **32**:377 (Sept.) 1935.

xanthomatosis, with serum cholesterol concentrations of 431 and 961 mg. per hundred cubic centimeters, respectively. Another daughter, aged 8, had a cholesterol level of 430 mg. per hundred cubic centimeters, with no manifestations of the disease.

No record exists, so far as we know, of another family such as ours in which, by a remarkable coincidence, both the mother and the father were hypercholesteremic, and of which 3 members maintained for many years an unquestionably high serum cholesterol concentration without evidence of xanthomatosis. It is not surprising that this union should produce 2 offspring with hypercholesteremia. More difficult to explain is the absence of unequivocal hypercholesteremia in the third son, H. R.

Several years ago Sperry[14] presented evidence indicating that in each healthy person a constitutional level of cholesterol is maintained within a relatively narrow range of variation. The results reported in this paper support that concept in a general way, in that each member of the family, with the possible exception of brother H. R., maintained a high level of cholesterol for many years; but the range of variation in each was considerably greater than that found for all but 1 of Sperry's 25 subjects. Despite this variability, the observations are not inconsistent with the hypothesis that the general level of cholesterol in the blood serum is inherited, and that the difference between normal families and those tainted with xanthomatosis is quantitative, rather than qualitative.

However, there is no direct quantitative relation between the development of xanthomatosis of the xanthoma tuberosum type and the concentration of cholesterol in the blood serum. The level of cholesterol is not the sole etiologic factor in this disease; there is no critical concentration above which xanthomatosis occurs and below which it is absent. This concept is well illustrated by J. J. (case 2), whose history was given in our previous report. Although this patient's serum cholesterol level was no higher, or possibly a little lower, than those of the mother, father and brother (D. R.) of patient H. R., he presented a typical picture of severe xanthoma tuberosum.[15]

Why did xanthomatosis develop in J. J. and not in H. R.'s relatives? Why does xanthomatosis occur in some persons with a relatively low concentration of cholesterol in the serum and not in others whose concentrations are relatively high? In searching for an answer to this question, we must consider the fact that xanthomatosis is the only one

14. Sperry, W. M.: The Concentration of Total Cholesterol in the Blood Serum, J. Biol. Chem. **117**:391 (Jan.) 1937.

15. It is difficult to compare many of the data in the literature because of uncertainty about the methods employed by various authors for the determination of cholesterol. The same method was used for all the analyses discussed in the present paper.

of the lipoidoses in which hyperlipemia has been demonstrated. In the other diseases in which abnormal quantities of lipids accumulate in various tissues, either the lipid is produced in the place where it is deposited, or, possibly, the tissues involved have an abnormal affinity for the lipid and remove it from the blood stream even in the absence of hyperlipemia. According to the latter concept, since the concentration of a constituent of the serum is a function of the rates at which it enters and leaves the circulation, no increase, or even a decrease, would be expected. The occurrence of xanthomatosis without hypercholesteremia, as in Schüller-Christian disease, may be explained in this way. On the other hand, when hypercholesteremia is present, the lipid may, so to speak, be forced into the tissue. The varying degree of susceptibility to xanthoma tuberosum in terms of the cholesterol concentration of the blood serum may be explained on the basis of the interplay of these two forces; the affinity for cholesterol in the tissues may vary from person to person, with a corresponding variation in the blood serum level at which the disease appears.

The foregoing hypothesis says nothing of the cause of hypercholesteremia. By what mechanism was the cholesterol level of patient H. R.'s blood serum maintained at a high level for thirteen years in the absence of any appreciable quantity of cholesterol in the food? There is abundant proof that in the normal mammal cholesterol is synthesized, destroyed and excreted via the intestinal tract. After an extended period during which no cholesterol is administered, the quantity of cholesterol in the body must be the resultant of these three processes, and presumably the cholesterol concentration of the blood serum reflects the balance among them. In Schönheimer's patient,[16] a defect in the excretion of cholesterol was proved to exist, and when she was placed on a cholesterol-free diet a prompt and large decrease in the cholesterol concentration of the blood serum took place. Apparently, the mechanism with which cholesterol is destroyed was able to cope with the quantity synthesized when the pressure of exogenous cholesterol was removed. In our patient the defect is either quantitatively or qualitatively different; either the mechanism for synthesizing cholesterol is hyperactive, or the two mechanisms for removing cholesterol are inadequate. Since the processes of synthesis and destruction almost certainly depend on enzymatic catalysis, it is reasonable to suppose that the basic hereditary defect is a failure to produce, or an overproduction of, one or more enzymes. Such a concept is in accord with current knowledge of inherited "errors of metabolism." [17]

16. Schönheimer, R.: Ueber eine Störung der Cholesterin-Ausscheidung, Ztschr. f. klin. Med. **123**:749, 1933.

17. Beadle, G. W.: The Genetic Control of Biochemical Reactions, in Harvey Lectures, 1944-1945, Lancaster, Pa., Science Press Printing Company, 1945, vol. 40, p. 179.

The genetic aspects presented by this family recently raised a difficult problem: Both the patient and his brother (D. R.) are contemplating marriage; and the brother, although he shows no clinical symptoms, is particularly disturbed by the prospect that his children may have xanthomatosis. A geneticist [18] whom we consulted gave the opinion that if the wife had a normal serum cholesterol level the chance of this occurrence would not be great, but if the wife should also happen to be hypercholesteremic, there would be a high probability of hypercholesteremia and xanthomatosis appearing in the children. The opinion was based on the likelihood that the trait is dominant.[19]

NOTE: The patient was married in the spring of 1948.

Lipid Phosphorus.—Little attention has been paid to lipids other than cholesterol in studies of xanthomatosis. In our most recent examination of members of the R. family, determinations of the lipid phosphorus concentration of the blood serum were included. (The range of variation in healthy persons with the method employed [20] has not been established with certainty, but it appears to be from 7 to 12 mg. per hundred cubic centimeters of serum.) It will be seen (table 2) that in our subjects the lipid phosphorus level was elevated, approximately in proportion to the elevation in the cholesterol concentration. This result might be taken to indicate that the abnormalities in respect to cholesterol represent only part of a general disturbance in lipid metabolism and regulation. On the other hand, the high concentrations of phospholipid may be secondary to the hypercholesteremia. Cholesterol and phospholipids are in some respects antagonistic, and there is evidence that the organism attempts to maintain a balance between them. It is also possible that the primary disturbance is in phospholipid regulation and that the hypercholesteremia is secondary.

Svendsen [11] also determined lipid phosphorus in his 34 subjects. No correlation in the values for cholesterol and phosphorus was evident, except in one respect: By far the highest lipid phosphorus concentration was obtained in the xanthomatous patient with definite hypercholesteremia.

Reference to 1 of the most striking cases on record should be made at this point. Herbert [21] reported on a girl 7 years of age with xanthomatosis, whose concentrations of cholesterol and lipid phosphorus in the

18. Dr. Franz J. Kallman, of the New York State Psychiatric Institute, made this statement.

19. Bloom and others.[10] Svendsen.[11]

20. Sperry, W. M.: Electrophotometric Microdetermination of Phosphorus in Lipide Extracts, Indust. & Engin. Chem. **14**:88 (Jan.) 1942.

21. Herbert, F. K.: A Case of Juvenile Xanthomatosis with Enlarged Liver and Spleen and Greatly Increased Plasma Lipoids, Arch. Dis. Childhood **18**:41 (March) 1943.

blood plasma were 2,600 and 203 mg. per hundred cubic centimeters, respectively. On a vegetable diet the concentrations dropped to 694 and 66 mg. per hundred cubic centimeters, respectively. These values are remarkable, not only because of the extreme hyperlipemia but also because the proportion of lipid phosphorus to cholesterol is so high.

Arterial Disease.—In many of the xanthomatous families described in the literature, arterial disease was a prominent feature, and many deaths from coronary thrombosis at an early age are reported. It is worthy of note, therefore, that no signs of arteriosclerosis were seen in our patient or in the other members of the family. A roentgenogram of the patient's pelvis showed no calcified areas in the vessels.[22] An electrocardiogram taken on Sept. 10, 1947 was normal.

SUMMARY

A patient with essential xanthomatosis of the xanthoma tuberosum type was observed for fifteen years, during thirteen of which he lived on a diet containing negligible quantities of cholesterol. Despite this regimen he continued to exhibit a pronounced hypercholesteremia, and no regression of the disease was noted. The only effects which may possibly be attributed to the cholesterol-free diet were a relatively small decrease in the average cholesterol concentration of the blood serum and the failure of any new lesions to appear.

Treatment with thyroid, insulin, lipocaic, vitamin B complex and ultraviolet radiation had no noticeable effect.

By a remarkable coincidence, the patient's mother and father were both hypercholesteremic, and 1 brother maintained an abnormally high concentration of cholesterol in his blood serum. In a second brother the serum cholesterol level frequently exceeded 300 mg. per hundred cubic centimeters but was within the range for supposedly healthy persons.

The observations on this family emphasize the heredofamilial nature of essential xanthomatosis and support the concept that an inherited hypercholesteremia is the primary disturbance in this disease.

17 East Eighty-Fourth Street (28).

22. Dr. A. Kean made the roentgenographic study.

EXPERIMENTAL PEANUT OIL PNEUMONIA IN RABBITS

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RAY BROOK, N. Y.

ASPIRATION of peanut kernels has been known for many years to produce a morbidity and mortality greater than that of many other similar agents.[1] In 1930, Heatly and Clausen [2] observed that simple ether extracts of roasted peanuts produced death in rabbits within seventy-two hours when injected intratracheally in amounts of 2 cc. Further investigation by these authors revealed the harmful fraction to be present in the unsaturated fatty acid of the oil extracted in this manner. However, Richards [3] reported that the clinical course of patients who aspirated peanut kernels failed to verify the severely toxic manifestations previously reported. Pinkerton [4] showed that simple neutral vegetable oils (iodized sesame seed and poppyseed oil and olive oil) produced practically no reaction and did not appear to injure the lungs in any way.

Thus, I became interested in studying the pathogenesis and mortality from peanut oil in lungs of experimental animals.

MATERIALS AND METHODS

Method 1.—Roasted peanuts without their skins were ground in a mortar, and the oil was extracted with twice their weight of ether. The mixture of ground peanuts and ether was then filtered through a gravity filter, and the ether was allowed to evaporate at room temperature. The residue was ground in a mortar, and the oil was extracted again as previously outlined. This procedure was repeated for a third time, and all the oil was pooled. The residue was mixed with distilled water to form a 15 per cent suspension and was set aside for control intratracheal injections.

Method 2.—Oil was extracted in like manner from roasted peanuts without their skins, using chloroform as the oil solvent.

Method 3.—Roasted peanuts were added to the skins of ten times the number of peanuts used (i. e., for each roasted peanut, skins from 10 roasted peanuts were

From the Department of Pathology, Duke University School of Medicine, Durham, N. C.

1. Jackson, C., and Spencer, W. H.: Arachidic Bronchitis, J. A. M. A. **73**: 672 (Aug. 30) 1919.

2. Heatly, C. A., and Clausen, S. W.: Experimental Studies in Peanut Bronchitis, Arch. Otolaryng. **11**:569 (May) 1930.

3. Richards, L., in discussion on Heatly and Clausen,[2] Arch. Otolaryng. **12**:845 (Dec.) 1930.

4. Pinkerton, H.: The Reaction to Oils and Fats in the Lung, Arch. Path. 5:380 (March) 1928.

added). These were ground in a mortar, and the oil was extracted with ether as in method 1. The residue was mixed with distilled water to form a 20 per cent suspension, which was set aside for control intratracheal injections.

PROCEDURE AND RESULTS

Rabbits were found to be the most satisfactory experimental animals. After light anesthesia was induced with ether, the hair over the anterior surface of the neck was closely clipped; the neck was painted with iodine and alcohol, and the peanut oil was introduced intratracheally

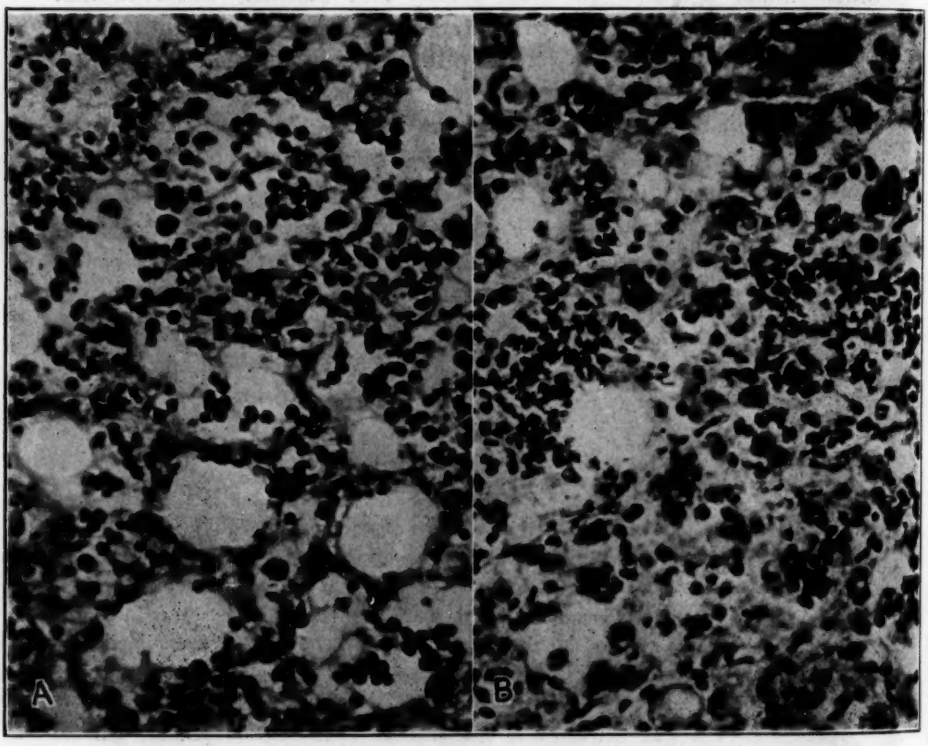

Fig. 1.—Photomicrographs of lung (*A*) from a rabbit autopsied twelve hours after intratracheal injection of oil, showing polymorphonuclear leukocytes, erythrocytes, fluid and an occasional large mononuclear cell; × 325; (*B*) from a rabbit autopsied forty-eight hours after intratracheal injection of oil, showing a definite increase in the cellular exudate. Note that the polymorphonuclear leukocytes are much more numerous than the large mononuclear cells; × 325.

with a straight no. 18 needle attached to a syringe. During the procedure the head and the neck were kept elevated to facilitate passage of the oil into the lungs and to prevent obstruction in the trachea. The animals were carefully watched and were autopsied within several hours of death, or were killed according to a prearranged schedule if they continued to live.

Group 1.—Eighteen rabbits were inoculated intratracheally with ether-extracted peanut oil (method 1). All received at least 2 cc. of oil except 4, 2 of these receiving 1 cc. and 2 receiving 0.6 cc. Aseptic technic was used throughout, and the oil was free of bacteria by cultural test. These animals were killed at twelve, twenty-four and forty-eight hours and at four, six, ten, thirty and sixty days, in order to study the pneumonic process through its various stages. The presence of the oil in the lungs was confirmed by taking roentgenograms after the injection and by staining the lungs with scarlet red after autopsy.

Animals autopsied twelve hours after intratracheal injection of oil showed grossly patchy areas of hemorrhagic consolidation which was slightly more pronounced on the right side. Microscopically, scarlet red and hematoxylin stains showed numerous large globules of oil in the alveoli. Hematoxylin and eosin stains showed an exudate of polymorphonuclear leukocytes, macrophages containing oil, erythrocytes, an occasional small round cell and fluid in the alveoli, the polymorphonuclear leukocytes predominating. These same elements were also quite prominent in the bronchioles and in the capillaries of the alveolar walls. There were only a few leukocytes in the mucosa of the trachea and bronchi.

Animals autopsied at twenty-four hours showed the same morphologic response as those killed at twelve hours, except that the exudate was slightly more abundant.

Forty-eight hour animals showed many alveoli and a few bronchioles packed with an exudate composed chiefly of polymorphonuclear leukocytes and fluid. These two elements reached their peak at this stage of the pneumonic process. In some areas a few of the polymorphonuclear leukocytes were undergoing karyorrhexis and karyolysis. Erythrocytes and macrophages were more numerous than at twenty-four hours. Many of the macrophages contained small globules of oil and granules thought to be cellular debris. Only a few small round cells were present. The alveolar walls were distended with a few polymorphonuclear leukocytes and macrophages, but the walls showed no other changes.

The pneumonic process at four days showed a definite diminution in the polymorphonuclear leukocytes, fluid and erythrocytes. The macrophages were much more numerous and in places completely filled the alveoli. The alveolar walls continued to be thickened with polymorphonuclear leukocytes, erythrocytes and a few macrophages.

At six days the macrophages reached their maximum, packing many of the alveoli. Alveolar fluid and erythrocytes were completely absent, and only an occasional polymorphonuclear leukocyte could be seen. The alveolar walls continued to be slightly distended with polymorphonuclear leukocytes, macrophages and erythrocytes. The bronchioles were not involved.

Animals autopsied on the tenth day after the injection showed numerous alveoli packed with oil-containing macrophages to the same degree as seen on the sixth day. An occasional polymorphonuclear leukocyte was present, but no fluid. The alveolar walls were slightly distended with erythrocytes and macrophages, but neither necrosis nor fibrosis was present.

Animals autopsied on the thirtieth day showed several small abscesses of the lung in which there were numerous polymorphonuclear leukocytes, gram-positive cocci in pairs and broken cellular debris, the abscesses being surrounded by a thick fibrous wall; however, the animals appeared

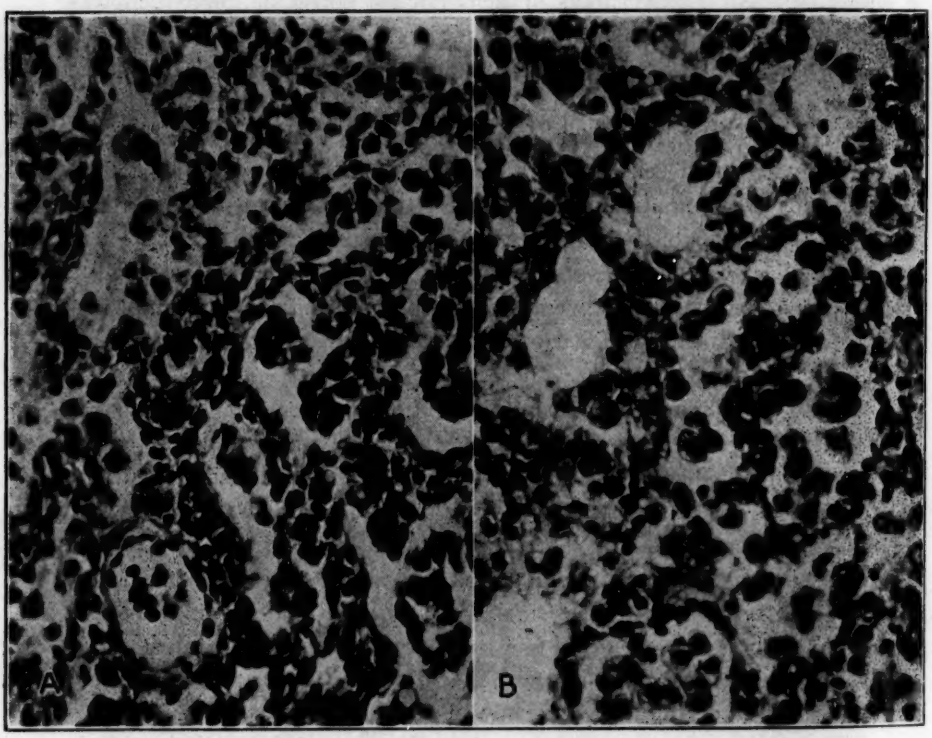

Fig. 2.—Photomicrographs of lungs from rabbits. *A* is from a rabbit autopsied six days after intratracheal injection of oil. Large mononuclear cells in the alveoli are more abundant. Only a few polymorphonuclear eosinophils are present; × 325. *B* is from a rabbit autopsied ten days after intratracheal injection of oil. Oil-laden macrophages are more pronounced here than in figures 1 *A* and *B* and 2 *A*; × 325.

thrifty and well at the time they were killed. There were many areas throughout the lungs not involved by abscess formation which showed only collections of macrophages containing fat. Here again the alveolar walls were thickened with macrophages and erythrocytes.

The only cells present in the alveoli sixty days after the intratracheal injection of oil were loosely scattered oil-containing macrophages,

which were much less numerous than at ten and thirty days. No other cells were present. There were only a few macrophages within the alveolar wall, the walls showing no fibrosis or other change.

Large globules of oil were most prominent in the alveoli of those animals autopsied shortly after inoculation, there being a gradual decrease in the amount of free oil within the alveoli as time elapsed. Oil was never observed in the regional lymphoid tissue. The mucosa of the bronchi and trachea showed the presence of only a few polymorphonuclear leukocytes during the acute inflammatory response. By the sixth day this was entirely absent. The graph shows the exudative

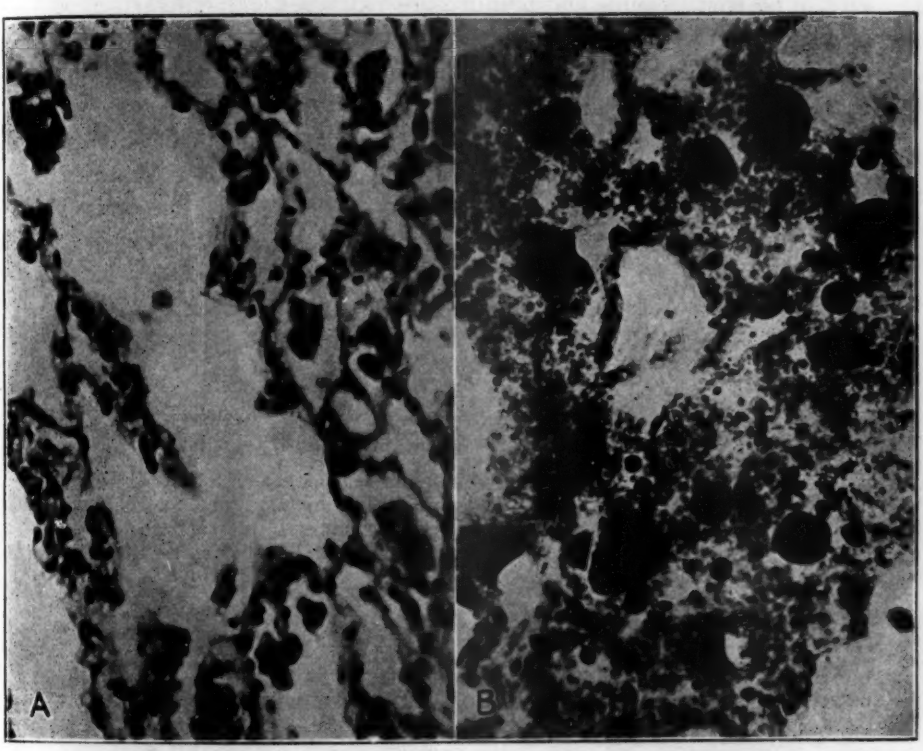

Fig. 3.—Lung from a rabbit autopsied sixty days after intratracheal injection of oil. Notice the definite decrease in number of large mononuclear cells and absence of other cellular exudate; × 325. *B*, fat stain showing oil in alveolar spaces, from a rabbit autopsied twelve hours after intratracheal injection of oil; × 162.

response as compared with duration of the disease process. Except in the 2 animals which showed pyogenic abscesses of the lung (autopsied on the thirtieth day), there was no pulmonary fibrosis, and in these 2 animals fibrosis was present only around the abscess areas.

Summary: Within twelve hours after intratracheal injection of oil, polymorphonuclear leukocytes and alveolar fluid were present to a

notable degree. There were only a few scattered macrophages at this time. At forty-eight hours the polymorphonuclear leukocytes and the alveolar fluid reached their maximum. The macrophages continued to increase, reaching their maximum on the sixth day and continuing in abundance through the thirtieth day. At sixty days they were quite prominent but had decreased considerably in number (see graph). The number of polymorphonuclear leukocytes and erythrocytes and the amount of alveolar fluid rapidly decreased from their maximum at forty-eight hours and were totally absent on the tenth day after injection.

Group 2.—Four rabbits were inoculated intratracheally with 2 cc. each of oil from peanuts and peanut skins extracted with ether (method 3) to see whether the addition of the peanut skins to the peanuts during the extraction of the oil might contribute any factor which would influence the course of the disease.

One animal died on the eighth day, and one died on the fifteenth day. The other 2 animals remained well, 1 being killed on the thirtieth

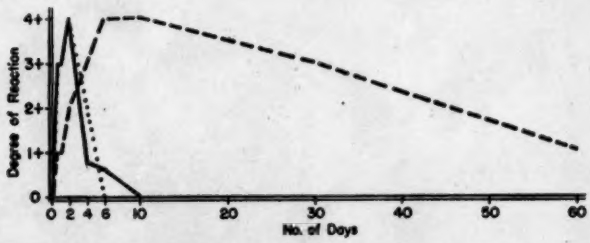

Fig. 4.—Graph showing exudative response as compared with duration of the disease process in rabbits given an intratracheal injection of ether-extracted peanut oil. The broken line indicates the relative number of macrophages present, the solid line the relative number of polymorphonuclear leukocytes and the dotted line the relative amount of exudative fluid.

day and 1 on the seventy-seventh. All the animals showed a macrophage response such as one would have predicted from the previously described experience, according to the duration of the intrapulmonary oil.

The colon and ileum of the animals which died on the eighth and fifteenth days were distended with gas and a foul-smelling, semiliquid fecal material. Microscopically, there was an acute inflammatory process involving the intestinal mucosa. In addition to the lipid pneumonia a mild interstitial pneumonia was present, characterized by polymorphonuclear leukocytes, fluid, erythrocytes and a few gram-positive cocci in pairs.

Group 3.—Three rabbits were given intratracheal injections of 2 cc. each of peanut oil extracted with chloroform (Method 2). These animals appeared thrifty and well at the time of killing on the seventy-seventh day. Grossly, the pleural surface showed no lesions, but on

section there were several small, light tan, firm areas. Microscopically, macrophages containing oil were seen within the alveoli, but no other cellular exudate or fluid was present.

Group 4.—Two rabbits were given an injection of 5 cc. of a 15 per cent suspension of the oil-free residue from the peanuts extracted with ether (method 1). These animals were autopsied on the fourteenth day, at which time they appeared thrifty and well. Gross examination of the lungs showed numerous small, firm, pearly gray areas of consolida-

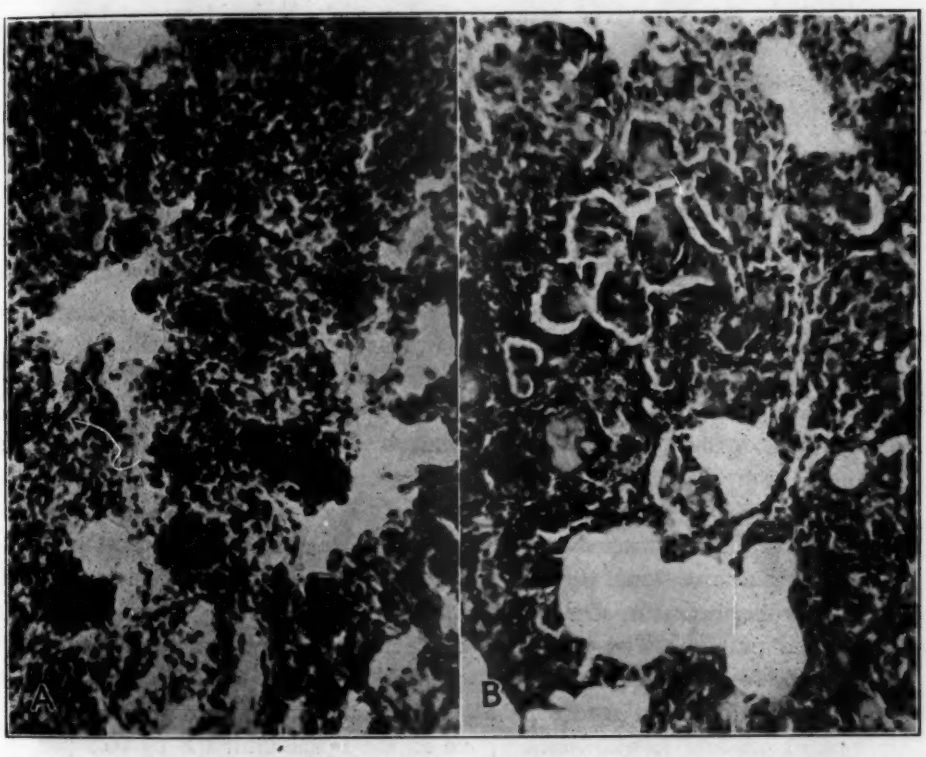

Fig. 5.—*A*, fat stain showing oil in alveolar spaces, from a rabbit autopsied sixty days after intratracheal injection of oil; × 162. *B*, photomicrograph of lung from a rabbit autopsied thirty-three days after intratracheal injection of a 20 per cent suspension of ether-extracted oil-free residue from the mixture of peanuts and peanut skins. In many of the alveoli is a fibrinoid material surrounded by large mononuclear and small round cells. Note the interstitial fibrosis; × 162.

tion. Microscopically, several small abscesses, composed of polymorphonuclear leukocytes, cells undergoing karyorrhexis and karyolysis and a few gram-positive cocci, were seen. These abscesses were surrounded in part by a thin layer of fibroblasts, and many of the closely adjacent alveoli were lined with a layer of low columnar epithelium. In many of the alveoli not involved in this abscess process a few macrophages,

small round cells, giant cells, a small amount of fluid and a pink fibrinoid material were observed, this material being interpreted as the oil-free peanut residue.

Two animals given intratracheal injections of 3 cc. of a 20 per cent suspension of oil-free residue from the mixture of peanuts and peanut skins extracted with ether (method 3) appeared thrifty and well at the time of autopsy on the thirty-third day. Grossly, the lungs showed a moderate, patchy consolidation which was most prominent on the posterior aspects of the lower lobes of both lungs. Microscopically, the alveoli in these involved areas showed a pink fibrinoid material surrounded by many large macrophages, giant cells and small round cells with an accompanying interstitial fibrosis. Cultures of these lungs at the time of autopsy yielded no pathogenic organisms.

COMMENT

Intratracheal injection of peanut oil produced an acute inflammation of the lungs which reached its maximum intensity at forty-eight hours; however, the death rate in the animals that received at least 2 cc. of oil was only 6.6 per cent at seventy-two hours. This compared with a death rate of 100 per cent within seventy-two hours in the experiments of Heatly and Clausen. However, 2 other animals died later, on the eighth and fifteenth days, respectively. In these 2 animals severe diarrhea with dehydration developed. At autopsy acute colitis and interstitial pneumonia were observed, death being attributed to secondary bacterial invasion.

Chloroform-extracted peanut oil and ether-extracted oil from peanuts and peanut skins, when injected, produced the same clinical courses and morphologic responses as the oil extracted with ether from skinless roasted peanuts. The immediate acute inflammatory process suggests that the free fatty acids present in peanut oil may be the exciting agent. Heatly and Clausen reported 0.5 per cent fatty acid in the free form in peanut oil, and Lewkowitsch [5] gave as the usual limit 0.8 to 16.5 per cent. The absence of polymorphonuclear leukocytes and fluid in the lungs after the tenth day shows the absence of progressive or delayed acute inflammatory reaction, thus suggesting absence of hydrolysis of the fatty acids to any extent. According to Lewkowitsch and other observers, hydrolysis depends principally on two factors—moisture and enzymes—and the rapidity of the reaction depends partly on the concentration of these two factors. The moist alveolar gases fulfil the first requisite, but experimental studies seem to indicate that vegetable oils are practically unaffected by the lipases present in the lung.

5. Lewkowitsch, J. I.: Chemical Technology and Analysis of Oils, Fats, and Waxes, New York, The Macmillan Company, 1909.

Pinkerton [4] showed that cod liver oil in the lungs does not have an immediately injurious effect because of the low initial acidity; however, this oil, in contrast to the vegetable oils, is rapidly hydrolyzed in the lungs, resulting in a reaction of large mononuclear and giant cells. As hydrolysis progresses, necrosis results. He also showed that liquid petrolatum, a pure hydrocarbon incapable of undergoing hydrolyis, is apparently sufficiently irritating to evoke a tremendous cellular reaction of large mononuclear phagocytes, with resulting connective tissue proliferation. The continued presence of numerous large fat-containing mononuclear phagocytes in the alveolar spaces of the animals in the present experiment suggests a similar irritative mechanism and an absence of production of free fatty acid by hydrolysis to any great degree since we encountered no necrosis. Another explanation for the continued presence of large collections of macrophages in the alveolar spaces in this experiment may be the slow hydrolysis of the free fatty acids; however, this hydrolysis was not sufficient to cause an acute inflammatory reaction or necrosis. It is interesting to note that Pinkerton's animals into which he injected iodized sesame seed and poppyseed oil and olive oil showed almost complete absence of a cellular response.

Peanut oil behaves like other vegetable oils in that it is not emulsified, since it was seen in large globules in animals killed as late as seventy-seven days after injection. The regional lymphoid tissues remained free of oil and oil-containing cells.

This experiment fails to support the work of Heatly and Clausen, but is rather in accord with the clinical observations of Richards and of Gittins,[6] who reported a low mortality rate in children following aspiration of peanut kernels. These authors suggested an absence of acute toxicity heretofore associated with aspiration of peanuts.

SUMMARY

Lipid pneumonia is produced in rabbits by intratracheal injection of peanut oil. The initial response is an outpouring of polymorphonuclear leukocytes, erythrocytes, macrophages, fluid and a few small round cells into the alveolar spaces. Within ten days this exudate is replaced completely by numerous oil-containing macrophages. Although macrophages persist in large quantities in the alveoli for seventy-two days, there is no apparent injury to the parenchyma of the lung except in those few cases with secondary infection.

The death rate at seventy-two hours in animals which received at least 2 cc. of intratracheal peanut oil is 6.6 per cent. The immediate outpouring of fluid, erythrocytes and polymorphonuclear leukocytes in

6. Gittins, T. R.: Peanut in the Bronchus of an Infant Aged Twenty-Two Months, Arch. Otolaryng. **11**:614 (May) 1930.

the alveolar spaces is thought to be due to the presence of free fatty acid in the peanut oil, but not in such concentration as to cause necrosis of the parenchyma of the lung. Peanut oil is sufficiently irritating to provoke a continued macrophage response.

The results of this experiment emphasize the absence of "marked toxicity" of peanut oil in the rabbit lung and support the more recent clinical observtaions of Richards and Gittins.

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RETARDATION OF POSTNATAL DEVELOPMENT OF KIDNEYS IN PERSONS WITH EARLY CEREBRAL LESIONS

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THE SERIES under investigation comprised 103 patients with mental deficiency from birth to 55 years of age. On most of these a complete autopsy was performed. The diagnoses of the cerebral lesions causing the mental deficiency were based on the autopsy observations, in addition to the clinical findings and the history. In the table, 87 cases in which microscopic material was available are summarized, with their etiologic origins shown in column 4. The statements in the table are of necessity brief and reveal little of the wealth of interesting information on which many of them are founded. They do demonstrate, however, that the series was quite heterogeneous with respect to the injury to the nervous system. In addition, the autopsy reports showed that there was no uniformity with regard to the extent of the lesions. In some patients a completely cystic brain weighing a few hundred grams was observed; in others the brain was of nearly normal weight and of almost normal gross and microscopic appearance. The degree of mental deficiency also varied greatly, with the patients ranging from idiots with an intelligence quotient of less than 0.10 (measured with the revised Binet test) to morons with an intelligence quotient of about 0.70. The majority of patients were idiots. The common denominator of the group was damage to the central nervous system, occurring either before or about the time of birth and severe enough to result in mental deficiency.

WEIGHT OF THE KIDNEYS

This investigation began with the observation that the kidneys of feebleminded patients at autopsy were frequently small, sometimes weighing as little as one third of normal without showing pathologic scarring or shrinkage to which the small size could be attributed. The question arose whether the low kidney weights could not be accounted for by the small body size of many patients. In order to determine this correlation, the arbitrary measure of "relative kidney weight" was established. This expressed in fractions of 1 the relation of the actual weight of the patient's kidney to the weight normal for his actual body size. This figure could not be obtained for adults, as no standard

From the Department of Anatomy, University of Louisville School of Medicine

Chronologic Correlation of Kidney Weights and Diameters of Renal Corpuscles in Patients with Cerebral Lesions

Case No.	Age	Sex	Etiology*	Data on Kidneys: Absolute Weight, Gm.	Data on Kidneys: Relative Weight	Data on Kidneys: Capsular Diameter, Range and Average, Microns	Comment
67	Birth	M	Anencephalus	30	About 1	65-100 (82)	
F1	Birth	M	Anencephalus	?	?	(79)	
153	4½ mo.	M	B	?	?	85-115 (102)	
96	10 mo.	F	P, H	44	About 1	75-102 (85)	
97	1 yr.	M	P?, M	39.5	0.73	70-95 (84)	
77	14 mo.	F	P, H	130	About 2	62-100 (86)	Polycystic kidney
84	20 mo.	F	P, H	63	0.76	88-112 (101)	
18	2 yr.	F	H, M	20	0.33	75-112 (96)	Body length, 65.5 cm.
157	2	F	M	36	0.59	75-147 (120)	Coaretation of aorta
78	2	F	?	74	0.69	78-115 (100)	
5	2	M	B, syphilis (?)	87	0.83	120-140 (131)	
21	3	M	P ?	75	0.81	93-135 (107)	
73	3	M	H, syringomyelia	100	About 1	99-113 (102)	
80	3	F	P, H	87.5	?	90-115 (105)	
76	4	M	Cystic brain	51	0.70	83-125 (108)	
121	4	M	Erythroblastosis fetalis	74	?	104-135 (119)	
181	4	M	?	65	0.62	?	Nephritis
108	4	F	B	?	?	120-145 (134)	
29	4	M	Erythroblastosis fetalis	100	About 1	107-130 (117)	
40	5	F	M, virus encephalitis ?	100	0.88	110-145 (130)	
79	5	F	P	74	Below 0.9	82-125 (112)	
16	5	F	B, H	75	0.61	102-152 (130)	Fetal lobation
114	5	F	P	52	Below 0.9	?	Cystic kidney
135	6	F	B ?	120	About 1	98-125 (109)	Nephrosclerosis
149	7	M	B, P	135	About 1	110-155 (130)	Fetal lobation Nephrosclerosis
183	7	M	P, M	77	0.76	105-135 (117)	
109	7	F	B	81	0.52	109-145 (130)	Microcolon; tall
156	8	F	?	79	Below 0.9	107-162 (136)	Malnutrition
38	8	M	Congenital syphilis (?)	120	0.78	105-145 (129)	
45	10	M	Porencephaly	90	0.69	103-145 (125)	
170	10	M	P, M	65	0.52	94-128 (110)	
174	10	F	P, B	110	?	108-140 (125)	
167	10	F	B	200	Above 1	106-158 (134)	
169	11	F	Hallervorden-Spatz syndrome	95	0.70	82-128 (113)	Odd kidney shape
98	12	F	B	135	?	95-145 (116)	
52	12	F	B	240	Above 1.2	143-177 (157)	
56	12	M	?	250	Above 1.4	130-163 (146)	Fetal lobation
48	12	M	P	135	Below 0.7	105-205 (164)	Tall (148 cm.) Nephritis
171	12	M	P	170	?	?	Diseased kidney
143	12	M	B, P ?	140	?	120-180 (141)	Fetal lobation
98	13	M	P ?, brain cyst	175	?	?	
175	13	M	B	135	0.77	88-128 (113)	
46	14	F	?, H, neurofibromas	?	?	109-154 (129)	Fetal lobation
64	14—	F	H, porencephaly	180	About 1	140-190 (158)	
74	15	F	P, M	155	0.87	119-162 (136)	
150	15	F	P, M	50	0.31	167-385 (255)	Left kidney weighed 8.3 Gm.
4	15	M	B ?	122	0.84	110-160 (126)	
37	15	M	F, moron	720	High	?	Nephritis
28	16	F	M, dwarf	125	0.85	106-163 (138)	Diseased kidneys
50	17	M	F, imbecile	166	About 1	110-142 (125)	Tuberculosis of kidneys
142	17	M	B	160	?	?	Nephritis
75	17	M	P, trauma	180	Below 0.8	?	Nephrosclerosis
49	19	M	F, imbecile, encephalitis	490	High	112-163 (141)	Nephrosis; congestion
44	19	F	F, imbecile	240	About 1	125-180 (152)	Tuberculosis of kidneys
51	19	F	F, moron	270	About 1	115-172 (149)	
62	19	F	P, imbecile	180	Below 0.9	110-175 (145)	
68	19	M	Congenital syphilis (?)	220	About 1	95-143 (121)	

Chronologic Correlation of Kidney Weights and Diameters of Renal Corpuscles in Patients with Cerebral Lesions—Continued

Case No.	Age	Sex	Etiology*	Data on Kidneys: Absolute Weight, Gm.	Data on Kidneys: Relative Weight	Data on Kidneys: Capsular Diameter, Range and Average, Microns	Comment
88	19	M	B, F ?	205	Below 0.9	137-178 (160)	Congested kidneys
59	21	F	F, imbecile	245	?	115-165 (144)	
92	21	M	F, spina bifida	(180)	?	127-188 (162)	No left kidney
96	21	M	F, spina bifida	?	?	?	Nephritis
138	21	M	M	109	?	116-161 (135)	Fetal lobation
43	22	M	Lindau's disease	280	About 1	96-140 (118)	Fetal lobation
128	22	M	?	110	Below 0.9	105-150 (131)	
30	23	F	B ?	150	Below 0.8	122-170 (145)	Nephrosclerosis
127	25	F	B, brain cyst	165	Below 0.8	122-170 (145)	
107	26	M	F, tuberosclerosis	?	?	133-188 (156)	
54	27	F	P	225	About 1	100-175 (132)	Nephrosclerosis
182	28	F	"Renal dwarf"	63	Below 0.5	190-270 (250)	Nephrosclerosis
86	29	F	F, moron	300	Above 1.1	165-220 (199)	Nephrosis
144	29	F	P ?	200	?	93-137 (115)	
26	31	F	?	155	Below 0.9	173-289 (232)	Right kidney weighed 15 Gm.
						Left only	Both kidneys diseased
110	31	F	F, imbecile	?	?	138-195 (167)	
63	32	M	B ?, colloid goiter	345	High	178-225 (201)	Edema
117	32	M	B, M	155	Below 0.8	119-175 (148)	Fetal lobation
33	33	F	P	?	?	118-162 (142)	
70	33	F	Congenital syphilis	233	About 1	100-138 (125)	
151	33	F	F	300	Above 1.1	?	Nephritis; edema
89	35	F	?	95	Below 0.5	?	Nephrosclerosis
60	36	F	F, imbecile	160	Below 0.8	?	Cystic kidneys
24	38	M	?	350	High	120-175 (151)	Renal infarcts
61	38	F	M, F ?	(r.120)	?	?	Tuberculosis of kidneys
105	39	F	F	(r.75)	?	120-175 (146)	Left kidney small
91	41	F	F, imbecile	241	About 1	113-148 (132)	Nephrosis
27	47	M	F, B ?	152	Below 0.8	144-190 (163)	
41	48	M	P, brain atrophy	300	?	?	Death from nephritis
34	48	M	H, F	100	Below 0.5	?	Nephrosclerosis; right kidney weighed 20 Gm.
39	55	F	F, imbecile	300	Above 1.1	132-188 (153)	Nephrosclerosis

* P indicates prenatal, abnormal development of the central nervous system; B, birth injury; H, hydrocephalus; M, microcephalus; F, familial hereditary mental deficiency.

values have been determined for the average kidney weights associated with different body lengths. In growing children, the relative kidney weight could be obtained because standard series were available which related the average weight of the kidneys to age and therewith, indirectly, to body length. For standard values, the tables of Coppoletta and Wolbach [1] were used. The kidney weights for persons from 12 years of age to adulthood were extrapolated from these tables. In addition, the extensive anthropometric tables of Engelbach [2] were used for

1. Coppoletta, M. M., and Wolbach, S. B.: Body Lengths and Organ Weights of Infants and Children, Am. J. Path. 9:55, 1933.

2. Engelbach, W.: Endocrine Medicine, Springfield, Ill., Charles C Thomas, Publisher, 1932, vol. 1.

reference. The two sets of values on body lengths are essentially in good agreement, the values of Coppoletta and Wolbach being slightly below the optimal values of Engelbach but well within the range determined by him.

An analysis of 98 cases of mental deficiency in which the kidneys were weighed resulted in the following figures: The kidney weight was below normal in 69 cases (71 per cent), if normal is regarded as ± 10 per cent of the average values of Coppoletta and Wolbach. In only a few cases could the low weight be attributed to the small body size of the patient, as is shown by the relative kidney weights. These could be determined in 66 cases (data on all of which are presented in the table). In 39 (59 per cent) of these cases the relative kidney weight was below 0.9; that is, these kidneys weighed less than nine tenths of the weight normal for the body length of the patient. Twenty-one cases were between 0.8 and 0.5 and 4 were below 0.5.

The number of small kidneys was greatest in the age group from birth to 10 years, in which 70 per cent (19 of 27 cases) showed relative weights below 0.9. In this group there were 6 cases within the normal range and 2 of greater relative weight. In the age group from 11 to 20 years, 53 per cent (10 of 19 cases) had a subnormal weight, while 21 per cent showed relative overweight. In the oldest group, from 21 to 55 years old, 50 per cent (10 of 20 cases) were below, and 30 per cent above, the normal range. As will be discussed later, this shift toward values above normal is an expression of pathologic changes, the incidence of which increases with age.

MICROSCOPIC ANATOMY OF THE KIDNEYS

As the small size of the kidneys could not be attributed to any gross pathologic changes or to the small body size of the patients, except in a few cases, an extensive microscopic investigation of 87 cases (see table) was undertaken. In the attempt to determine whether development proceeded normally, comparisons were made with the normal features of development as described in the literature and as observed in 8 controls 1 week to 2 years of age. Suitable control material was not available for the ages from 2 to 12 years, but 14 controls from 12 to 45 years of age were investigated. The following criteria were found especially useful in the determination of the state of development of the kidneys: (1) the state of differentiation of the cells covering the glomerular tuft; (2) the diameter of the renal corpuscles; (3) the difference between the diameters of peripheral and central corpuscles; (4) the size of a glomerulus-free zone under the renal capsule, and (5) the diameter of the renal tubules. The observations with respect to each of these criteria are reported in the following paragraphs. For

details of the normal development, reference is made to the papers of Külz [3] and Moberg [4] and to the summaries of von Möllendorff [5] and Peter and associates.[6]

1. At birth all peripheral glomeruli and a varying proportion of central glomeruli are covered with a continuous layer of cuboidal epithelium. Normally, this covering soon becomes discontinuous and disappears in a way not yet beyond discussion, until the glomerulus has the usual appearance of capillary loops separated by clefts and covered by a few squamous cells. The change is normally completed by the age of 2 years. In the controls no cuboidal epithelium could be found beyond 14 months of age. In the patients with cerebral damage less than 2 years old, all kidneys showed a great number of glomeruli with cuboidal epithelium. Furthermore, this infantile feature was observed in 12 of 16 patients from 2 to 5 years of age, in 2 of 10 from 6 to 10 years, in 4 of 25 from 11 to 20 years and in 1 patient 29 years of age. While in persons of the lower age groups many glomeruli have a truly fetal appearance, with a continuous edge of dark nuclei surrounding the capillary loops, in older persons only a few loops are usually covered in this way and the rest of the glomerulus appears mature. The cuboidal epithelium is easily distinguished even under low magnification because of the rows of dark nuclei (fig. 1 *A* and *B*).

2. The diameter of the renal corpuscles was determined from sections by means of an eye piece micrometer. In most of the younger patients 40 corpuscles were measured, 20 in the peripheral and 20 in the central portion of the cortex. The measurements were carried out on corpuscles of healthy appearance which showed the vascular pole and a thin Bowman's capsule, indicating that the section was not peripheral. Two capsular diameters at right angles to each other were determined and the mean taken of these. This procedure agrees in all essentials with that employed by most authors.

The renal corpuscles normally grow from 70 to 100 microns at the time of birth to about 200 microns in the adult. The results of the measurements are reported in form of a chart, which also contains the control values obtained.

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3. Külz, F. O. L.: Untersuchungen über das postfötale Wachsthum der menschlichen Niere, Inaug. Dissert., Kiel, Naumburg, a. S., G. Pätz, 1899.

4. Moberg, E.: Anzahl und Grösse der Glomeruli renales beim Menschen nebst Methoden diese zahlenmässig festzustellen, Ztschr. f. mikr. anat. Forsch. **18**: 271, 1928.

5. von Möllendorff, W. V.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1930, vol. 7, p. 1.

6. Peter, K.; Wetzel, G., and Heiderich, F.: Handbuch der Anatomie des Kindes, Munich, J. F. Bergmann, 1928, vol. 2, p. 1.

Figures 1 to 4

3. At birth, the youngest generation of renal corpuscles is located in dense arrangement directly under the renal capsule. These corpuscles are smaller than the older and more central ones. Normally, however, the difference soon disappears. All authors agreed that after 2 years of age the glomeruli do not vary greatly throughout the kidney. Moberg [4] reported disappearance of the difference in size at 2 months. The present series of controls showed no appreciable difference after the age of 14 months. In the mentally deficient persons, the peripheral glomeruli remained conspicuously smaller in a majority up to 10 years of age. In addition, there was the following variation in the degree of differentiation: The glomeruli which retained the cuboidal epithelium were almost invariably found in the peripheral regions of the cortex (figs. 3 and 4).

4. The cortex corticis (Hyrtl) is a zone free of glomeruli which lies under the capsule of the kidney. It arises during the first months after birth when the tubules grow in length and expand beyond the youngest and most peripheral generation of glomeruli. In the normal kidney, glomeruli are rarely seen directly under the renal capsule after the age of 1 year. In most of the mentally deficient patients the cortex corticis was narrow. It rarely reached the normal width of 0.4 to 0.9 mm. in the adult. Even in older patients glomeruli were often seen directly under the renal capsule (fig. 6).

5. The renal tubules increase not only in length but also in width throughout infancy and childhood. Representative values are 18 to 37 microns for the diameter of the proximal convoluted tubules at birth as compared with about 57 microns in the adult. The diameter of the proximal convoluted tubules was measured in 40 of the cases in the table, but the measurements are of doubtful value in many instances because terminal conditions and even slight imperfections of preservation influence the tubules far more than the glomeruli. For several cases, however, there is little doubt that the tubules were abnormally narrow: the average diameter in case 77, 14 months of age, on 20 measurements was 33 microns; in case 84, 20 months of age, 34 microns; in case 18, 2 years of age, 36 microns; in case 80, 3 years of age, 37 microns; in case 76,

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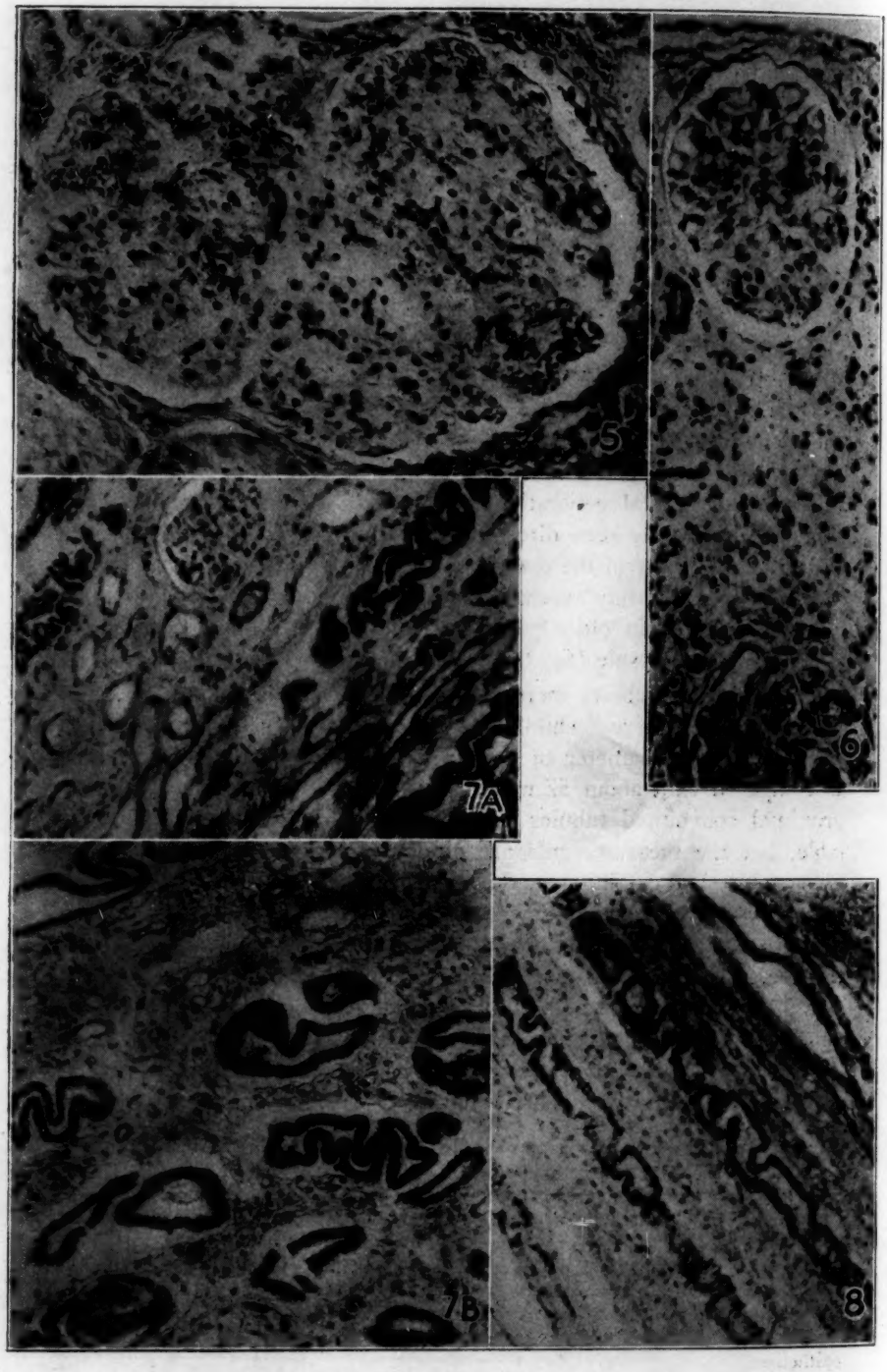
Fig. 1 (case 67: newborn infant with anencephalus).—*A*, medullary ray reaches the capsule at right. *B*, fetal appearance of glomeruli, which are densely arranged directly under capsule. The picture is that of a normal kidney at birth; × 250.

Fig. 2 (case 175: idiot, 13 years of age).—Three glomeruli near the capsule. The lowest is degenerative with only a few capillary loops: the middle one is normal but small; the upper one (arrow) is almost completely hyalinized and atrophied; × 250.

Fig. 3 (case 157: idiot, 2½ years of age).—Glomeruli are densely arranged under the capsule. They are very small and partly degenerating. Rests of cuboidal epithelium may be seen on the capillary tufts; × 250.

Fig. 4 (case 183: idiot, 7 years of age).—Glomerulus with typical cuboidal epithelium.



Figures 5 to 8

4 years of age, 34 microns; in case 135, 6 years of age, 41 microns; in cases 183 and 109, 7 years of age, 38 microns; in case 45, 10 years of age, 41 microns; in case 170, 10 years of age, 40 microns.

Degenerative phenomena play a great part in the picture of the kidney development in patients with early cerebral lesions. While this is not the place to give a detailed account of the pathologic findings, some of the principal changes are described briefly. In the 5 patients less than 5 months of age occasional degenerative glomeruli were seen which showed only a few small capillary loops; others were partly or totally hyalinized and often had fibrous rings surrounding Bowman's capsule. The corresponding nephrons usually showed signs of atrophy, so that small areas of devastation arose which were located mainly in the peripheral parts of the cortex. As will be discussed later, these observations as such are probably not abnormal for infants. A patient (case 77) 14 months of age was the youngest to show the severer changes. The kidneys were polycystic and much overweight because of many large cysts filled with fluid. Many glomeruli showed varying stages of hyaline degeneration. Those glomeruli which appeared otherwise normal were small and the smallest ones were covered with cuboidal epithelium. It was characteristic in this patient, as in many of the older ones, that the degenerative changes were not seen throughout the kidney but that they occurred in small areas. Atrophy of single nephrons with the neighboring nephrons intact was often observed (fig. 2). Scattered degenerative and atrophic areas were observed in many patients in the age group below 10 years (fig. 3), but only 5 of the 39 in this group were actually severely diseased. This picture changed with advancing age. Ten of 25 patients from 11 to 20 years of age showed severe renal lesions. Typical chronic glomerulonephritis was seen in 3 and tuberculosis in 2 of these patients, these conditions being superimposed on degenerative changes. In patients older than 20 years not a single kidney presented a completely normal picture. In the table the cases with gross lesions are indicated, but those in which no definite diagnosis of a renal "disease" was made almost invariably showed scattered foci of degeneration, sclerosis and atrophy, in addition to signs of retarded development in many.

Fig. 5 (case 150: idiot, 15 years of age).—Giant glomerulus from a small kidney The magnification is the same as that in figure 7; × 250.

Fig. 6 (case 127: idiot, 2 years of age).—Well developed but small glomerulus directly under the capsule; × 250.

Fig. 7 (case 77: idiot, 14 months of age).—*A*, tortuous collecting tubules in the medullary rays; × 140. *B*, collecting ducts in the medulla. Oblique section; × 140.

Fig. 8 (case 78: idiot, 2 years of age).—Collecting ducts in the medulla. Longitudinal section; × 140.

The kidneys of 2 children with anencephalus at birth revealed no significant abnormalities of growth and differentiation (fig. 1 *A* and *B*). In 5 cases many of the collecting ducts showed a tortuous course (figs. 7 and 8). The possible significance of this fact is discussed later. In the entire series 8 patients had fetal lobation, and 3 had polycystic kidneys. In 1 patient the left kidney was congenitally missing. In 2 patients (cases 150 and 26) one kidney was much smaller than the other (see table).

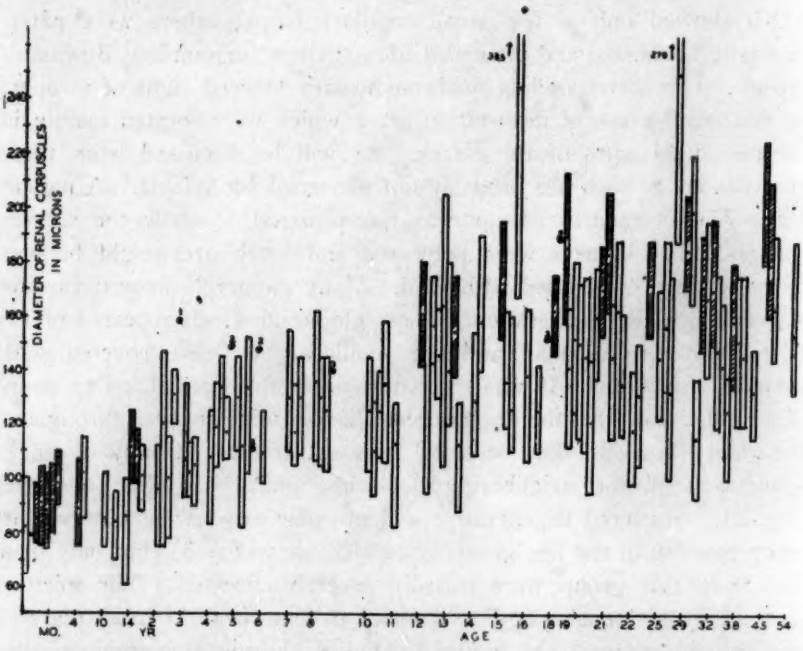


Fig. 9.—Each column represents the range of capsular diameters in an individual case; each dot represents an average value. Columns for cases with cerebral lesions are white, for control cases crosshatched. Points with small numbers are values from the literature: 1, indicates Külz, 2, Eckhardt, and 3, Moberg.

Case 150 will be described in detail because of its possible implications.

The patient was a 15 year old girl with multiple developmental malformations and neurofibromatosis. She died, not of renal disease, but of bronchopneumonia. She was an idiot, with a small head and a brain which weighed only 810 Gm. The left kidney weighed 8 Gm., the right 42 Gm. With consideration of the small size of the patient, the combined weight of the kidneys was still less than one third of the norm. Grossly, the right kidney appeared only slightly abnormal except for its small size. The left kidney was spherical and little more than walnut sized. The capsule was smooth. After it was stripped, the surface of the kidney appeared slightly granular. On section no difference between medulla and cortex was apparent. Microscopic examination showed sclerotic and degenerative changes, mainly in the larger kidney. In both kidneys, however, the glomeruli were abnormally large, measuring up to 385 microns in diameter (fig. 5). The largest glomeruli

were in the most central portion of the cortex in both kidneys. In these giant glomeruli the connective tissue as well as the capillary tissue was increased in amount. Cuboidal epithelium was absent. Bowman's capsule was not thickened around most of the corpuscles. It is a remarkable fact that these kidneys, which were relatively the smallest of the whole series, possessed glomeruli larger than any reported before.

COMMENT

Diameter of Renal Corpuscles.—The picture of retardation of development as demonstrated in the preceding pages is a composite view. No single criterion in any single case established the diagnosis of retardation. The most important criterion for practical purposes is probably the diameter of the renal corpuscles, provided the validity of certain standard values can be assured. In general, the control values obtained in the course of this investigation are in good agreement with the values of other authors. Eckardt [7] measured the glomeruli in 8 cases and Moberg [4] in 32 cases. Both authors obtained their measurements from sections. Külz [8] measured the glomeruli in macerated preparations from 12 cases. Other values in the literature are given as averages and without mentioning the ages of the subjects.

The control values for the present study came from 22 persons and should be considered the most reliable standard for comparison, because the kidneys were preserved and measured in exactly the same way as those of the patients with cerebral lesions. Moberg's values were consistently lower than those of any other author. It is possible that he measured the glomeruli proper (capillary tufts) instead of the renal corpuscles (capsular diameters). Moberg postulated that the methods of others, which were perhaps less accurate than his own, should produce lower values,[8] but he never explained the contradictory fact that all the other values reported are actually higher than his own. If the values obtained from patients with cerebral lesions are compared with all available standard values (chart) a majority falls clearly below the normal curves. Even when compared with the lowest standard values, those of Moberg, nearly half of the patients are subnormal. It is of some interest that one of Moberg's patients, an 11 year old boy, showed an average glomerular diameter of 124 microns, which is extremely small even in Moberg's series. This boy had epilepsy and was reported a suicide. There is no record of the condition of his brain. In the present control series the values obtained from a 4 month old boy (average capsular diameter, 89 microns) appear very low. The autopsy report revealed that congenital malformations were observed, but no report on the state

7. Eckardt, C. T.: Ueber die compensatorische Hypertrophie und das physiologische Wachsthum der Niere, Virchows Arch. f. path. Anat. **114**:217, 1888.

8. Moberg,[4] p. 276.

of the central nervous system was available. It is possible that this child should be in the series of patients rather than in the control series.

The range of sizes of the renal corpuscles in the normal adult kidney does not exceed 50 microns and would probably be still smaller if one could be sure that the greatest diameter was measured in every instance. Brodie and MacKenzie [9] pointed out that the capsular diameter rises with the increased activity of the glomerulus. In eleven experiments on cats, the average change in size, as reported by these authors, was 15 per cent. This is well within the range of sizes normally seen in adult kidneys, and it is quite possible that the differences in size of the normal glomeruli can in part be attributed to a difference in the functional states. In the kidneys of patients with lesions of the brain there is often a great difference in the sizes of the renal corpuscles, which is the result of a number of factors. In the first place, as has been pointed out, the peripheral glomeruli do not expand at their normal rate and, therefore, remain smaller than the central ones. Secondly, some glomeruli usually appear of almost normal size even in kidneys in which the average size of the glomeruli is small. It is impossible to decide whether some kind of hypertrophy (perhaps "compensatory") of individual glomeruli is present in all these cases. On the other hand, hypertrophied glomeruli do occur, for instance, in cases 150 and 26. Eckardt [7] described glomeruli up to 322 microns in diameter, which he regarded as hypertrophic.

Degeneration and Retardation.—In the abnormal development of the kidneys it is difficult to separate completely the phenomena of degeneration and retardation. The delay of differentiation, which is indicated by the persistence of the cuboidal epithelium over the glomeruli, is undoubtedly a phenomenon of true retardation, but the decrease in growth rate shown in the development of the cortex corticis or in the expansion of the glomeruli could be produced by true retardation or by gradual degeneration and atrophy. Degenerative phenomena are frequent in normal development. Pohl [10] named degeneration of glomeruli as one of the fetal criteria which are still regularly seen during the first year of life. Herxheimer [11] reported hyaline changes in the glomeruli of 80 per cent of children less than 1 year of age. He regarded them not as results of inflammatory processes but as small developmental

9. Brodie, T. G., and MacKenzie, M. B.: On Changes in the Glomeruli and Tubules of the Kidney Accompanying Activity, Proc. Roy. Soc., London, s.B **87**: 593, 1914.

10. Pohl, W.: Ueber Ausreifung der Niere: Unreife und krankhafte Bildungen in Säuglingsnieren, Inaug. Dissert., Greifswald, H. Adler, 1909.

11. Herxheimer, G.: Ueber hyaline Glomeruli der Neugeborenen und Säuglinge. Frankfurt. Ztschr. f. Path. **2**:138, 1909.

errors ("Irrungen"). Schwarz [12] reported that 30 per cent of a series of infants less than 3 weeks old had foci of devastation in the renal cortex and many other changes, which he attributed to the secretion of toxic substances in the newborn. Finally, Friedman, Grayzel and Lederer [13] again described the frequent lesions in the kidneys of newborn and stillborn infants as involving the arterioles and the glomeruli and pointed out their focal distribution and the fact that only microscopic examination will reveal these changes. These authors recognized that the lesions are not associated with any clinical syndrome and showed that their cause and significance are not understood, although they are congenital and perhaps of vascular origin. They called the syndrome "congenital glomerulosclerosis." Normally, the degenerative foci apparently end in complete atrophy and are rarely observed in older persons. In patients with cerebral lesions they appear to increase with age, the old foci gradually degenerating and new ones appearing. It should be pointed out, however, that many areas of the kidneys are usually unaffected by hyaline, sclerotic or vascular changes, but that even these unaffected areas may show the signs of retardation of development. One gains the impression that retarded areas are not necessarily doomed to degeneration and atrophy but that the probability of their becoming involved in such changes increases with age and is the greater the severer the retardation.

Differences in Retardation of Different Parts.—There is accumulated evidence that the retardiation of development is greatest in those structures of the kidney which are ontogenetically the youngest. The peripheral glomeruli show lack of growth and differentiation in a much more conspicuous way than do the central ones. The final generation of glomeruli arises in the most peripheral cortex not long before birth. At birth, these are still in an undifferentiated condition as compared with the central glomeruli, the oldest of which have existed for months. In fact, the oldest generation or two have degenerated and disappeared by the time of birth. Normally, the peripheral glomeruli must expand somewhat faster than the central ones, as both attain about the same average size by the age of 1 or 2 years. In patients with lesions of the brain a differential apparently is present in the retardation of normal growth rates which results in the abnormally long persistence of the difference in size between younger and older glomeruli.

The few cases which showed coiled collecting ducts can perhaps be explained by a difference in the rate of retardation between the collecting

12. Schwarz, L.: Weitere Beiträge zur Kenntnis der anatomischen Nierenveränderungen der Neugeborenen und Säuglinge, Virchows Arch. f. path. Anat. **267**:654, 1928.

13. Friedman, H. H.; Grayzel, D. M., and Lederer, M.: Kidney Lesions in Stillborn and Newborn Infants; "Congenital Glomerulosclerosis," Am. J. Path. **18**:699, 1942.

ducts and the nephron. The collecting ducts, and particularly the papillary parts, are probably the first parts of the kidney to differentiate. These are the parts most affected by the folding and coiling. The interpretation might be that the ducts are less retarded than the rest of the tissues and that their disproportionate growth in length causes the coiling. The fact that the few measurements of papillary ducts which have been carried out showed no decrease in diameter, even in kidneys with very small glomeruli and convoluted tubules, seems to confirm this view.

Cerebral Lesion and Renal Development.—The evidence presented in this paper points to a considerable and almost general decrease in the rate of postnatal development of persons who have deficiencies of the brain tissue in early life. Even if the deficiencies existed from early fetal stages on, as they do in cases of hereditary feeblemindedness or congenital malformations of the brain, the kidneys appear unaffected until the time of birth. It is significant that the 2 newborn infants with anencephalus who were studied showed kidneys of approximately normal size and state of differentiation. If damage to the brain exerts an influence on the prenatal development of the kidneys, this influence should be manifest in persons who are practically deprived of brain tissue at early embryonic stages. Therefore, from these 2 cases conclusive proof is obtained that whatever the influence of cerebral lesions on development of the kidneys it is not significant before birth. In addition, the data show that retardation of kidney development is still inconspicuous during the first few months after birth, if it exists at all. When the series is surveyed chronologically, it becomes clear that development becomes progressively out of step with the rest of the body during the first two years of life, that is, during a period of rapid growth of the child. The growth of the kidneys is disproportionately retarded. Body length and the weights of liver, spleen and heart often show subnormal values in patients with brain lesions, but never proportionate to the lack of growth shown by the kidneys.

A discussion of the possible mechanism of an influence of the nervous system on kidney development must necessarily be speculative. The theory that the endocrine glands might be mediators in this mechanism cannot be excluded. It is well known (as, for instance, shown by Selye, Stone, Nielsen and Leblond [14]) that the anterior pituitary hormones and others have a direct influence on the growth of glomeruli and tubules, and it is a fact that many mentally defective persons show conspicuous deficiencies of the pituitary, thyroid and adrenal glands. On the other

14. Selye, H.; Stone, H.; Nielsen, K., and Leblond, C. P.: Studies Concerning the Effects of Various Hormones upon Renal Structure, Canad. M. A. J. **52**:571, 1945.

hand, obvious cases of hormonal deficiencies (such as mongolism and cretinism) were not included in the present series. The influence of the hormones on growth is certainly beginning during fetal life.[15] Therefore, the reason the retardation of development begins to make itself felt only after birth would still have to be explained. The importance of the central nervous system as a growth-regulating factor has been variously estimated. Rössle,[16] in his discussion of the relation between general and specific disturbances of growth, was inclined to attribute a considerable influence to the brain. *"Ganz unklar ist ferner die Rolle des Gehirns; ich möchte es selbst als Wachstumsorgan ziemlich hoch einschätzen."* ("In addition, the role of the brain is quite unclear; I myself would evaluate it as a rather important organ of growth.") In my opinion, a direct influence of the nervous system would possibly explain the fact that the retardation of development in persons with lesions of the brain becomes apparent sometime after birth, as the nervous regulation of the body becomes more and more dominant. A possible factor in the mechanism of this influence is vascular changes. Although this series of cases offers no conclusive evidence of such changes as the cause of retardation in the development of individual nephrons, the methods used were not adequate for a solution of this problem.

It is not surprising that the correlation between the severity of the cerebral lesions and the degree of retardation of development is not rigid in this heterogenous series. The smallest and most severely retarded kidneys were usually seen in patients with severe malformations or other brain lesions, but even in these cases no correlation with the location of the cerebral damage or with the time at which it occurred could be proved. Some of the most obvious cases of retarded development were observed after birth injuries to the brain, others after prenatal damage.

SUMMARY

One hundred and three persons with mental deficiency who had lesions of the brain before or at the time of birth were investigated with respect to the development of their kidneys. The great majority of the kidneys were abnormally small without pathologic changes which could fully account for the smallness. Microscopic examination revealed retardation in differentiation and growth of glomeruli and tubules after birth. Prenatal development is not delayed, as is shown by 2 newborn infants with anencephalus, the kidneys of whom appeared to be in a normal state of growth and differentiation. The retardation becomes

15. Windle, W. F.: Physiology of the Fetus: Origin and Extent of Function in Prenatal Life, Philadelphia, W. B. Saunders Company, 1940.

16. Rössle, R.: Wachstum und Altern: Zur Physiologie und Pathologie der postfötalen Entwicklung, Munich, J. F. Bergmann, 1923.

most conspicuous after the first year of life. It is disproportionate in that other organs and general bodily growth are much less affected than the kidneys. Degenerative changes with which all retarded kidneys are afflicted become more pronounced as the age of the person advances. In older patients they usually lead to severe pathologic changes.

It is concluded that early cerebral lesions retard the development of the kidney after birth through an unknown mechanism.

The material presented in this paper was collected at the Wallace Research Laboratory of the Wrentham State School, Wrentham, Mass., by Dr. Clemens Benda. Control material was supplied by Dr. Benjamin Castleman, Dr. C. Tedeschi and Mr. S. Holt.

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Progress in Pediatrics

CONGENITAL PSEUDARTHROSIS OF THE TIBIA AND ITS RELATION TO FRAGILITAS OSSIUM

Report of a Case and Review of the Literature

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PSEUDARTHROSIS, or pseudoarthrosis, implies the formation of a false joint, usually following a fracture, with no attempt at repair. It occurs in both adults and children, and the paucity of descriptions for all types of the condition in the majority of textbooks bespeaks its comparative rarity. The sites of election are mainly confined to the following bones: the tibia or fibula, usually the lower part, and less often the upper third of the femur, the upper and middle thirds of the clavicle and humerus and the lower part of the forearm (Kelly [1]). Blumenfeld [2] stated:

> In accordance with Bruns's statistics, quoted by Böhler, pseudarthrosis occurs once in 200 or 250 cases, or in 0.5 per cent of all diaphyseal fractures; according to Scudder, it occurs in from 2 to 3 per cent; and according to Hey Groves, in from 4 to 5 per cent.

Milch [3] reported that nonfusion or separation of the capital epiphysis of the hip from various causes may result in so-called epiphysial pseudarthrosis. Although the adult form of pseudarthrosis of the long bones is usually amenable to surgical treatment, the juvenile form, for some peculiar reason, is particularly refractory. Especially unyielding to treatment is that form which occurs in the leg in infancy or childhood associated with deformity and usually with atrophy of one or more bones and called congenital pseudarthrosis of the tibia. The rarity of this condition can be gaged from the fact that Blumenfeld's series of 135 cases of pseudarthrosis of the long bones included not a single instance of congenital pseudarthrosis of the tibia. In most of these congenital cases, only the tibia is affected; less often both the

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1. Kelly, S. W.: Surgical Diseases of Children, St. Louis, C. V. Mosby Company, 1929, vol. 1, p. 465.

2. Blumenfeld, I.: Pseudarthrosis of the Long Bones, J. Bone & Joint Surg. **29**:97-106 (Jan.) 1947.

3. Milch, H.: Epiphyseal Pseudarthrosis, J. Bone & Joint Surg. **24**:653-662 (July) 1942.

tibia and the fibula are involved, and rarely the fibula alone. Occasional reports show that the congenital form may occur in the femur, clavicle or ulna. The purpose of this paper is to present a case of congenital pseudarthrosis of the tibia and to draw attention to its probable relation to fragilitas ossium.

REPORT OF CASE

A French boy 15 years of age, born in Tientsin, China, was admitted to the Peiping Union Medical College Hospital Jan. 25, 1938 on account of fracture of the left leg caused by repeated trauma for the past twenty-five months. From

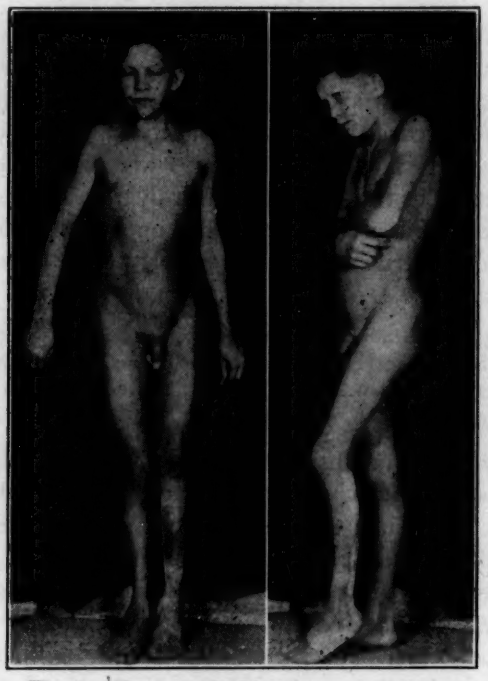

Fig. 1.—Front and side views of patient.

birth, he was said to have had weak, thin legs. He began to walk at the age of 1 year and had had no trouble with locomotion until twenty-five months before admission, when he was struck in the lower part of the left leg with a football. This accident necessitated two weeks of rest in bed. One month later he again injured his left leg in a fall and rested in bed for ten days, but he walked with a slight limp after this accident. A month later, after a kick in the left leg during a game of football, a physician discovered that he had a fracture of the left tibia and fibula, and immobilized the left limb in a plaster cast. The fracture was said to have nearly healed in good position, but little callus was evident at an examination two months later.

Four months after this examination, the patient fell from a wall and had to stay in bed for a while, but he was soon able to walk about with the aid of a stick.

About a month later, the fracture of the tibia was said to have nearly healed, but the bone appeared atrophic and crooked. This condition resulted in a picture of pseudarthrosis of the left tibia, for which operation was performed in May 1937, with removal of bone. The patient's left leg was then immobilized in a plaster cast until January 1938, when the pseudarthrosis was observed still to be present. A short time later, after removal of the cast in the Peiping Union Medical College Hospital, the fracture of the left tibia, which was extremely tender, could be felt at a point about 13 cm. above the internal malleolus. Physical examination showed that the left lower extremity was moderately atrophic and shorter than the right (fig. 1).

Roentgenograms revealed considerably more deformity of the bones than was suggested from physical examination (fig. 2). The left tibia was moderately

Fig. 2.—Roentgenograms of both legs. The middle roentgenogram represents the anteroposterior view of the right leg, while the pictures at the right and left show the anteroposterior and lateral views, respectively, of the left leg.

atrophic and showed an ununited fracture just above its lower fourth. The fractured ends were separated by a slightly oblique zone, made up of tiny radiolucent areas. The fractured ends were ragged, and the superior one was slightly broader, as though to accommodate the lower one. Moderate lateral and backward angulation of the left tibia was present. The left fibula was decidedly atrophic, especially in its lower half, in which there was moderate medial and posterior angulation. At about the level of the fracture of the left tibia, the left fibula appeared slender with pronounced thinning of its cortex and an appearance suggestive of a healed fracture. Both these bones were moderately osteoporotic. The right tibia was slightly atrophic, with mild medial and posterior bowing of its upper third and with evidence of an incomplete fracture. The right fibula was slightly atrophic, with an old healed fracture showing an acute medial angulation at

the junction between the middle and the lower third. Both bones, however, were of normal density. There were a few dense transverse lines in the diaphysial ends of both tibias. All the epiphysial lines appeared regular. Both knee and ankle joints were normal.

The blood calcium measured 10.2 mg., the inorganic phosphorus, 5 mg., and the phosphatase, 3.9 units per hundred cubic centimeters. The Wassermann reaction of the blood was negative.

Operation was performed in February 1938 by Dr. C. M. Meng, of the orthopedic service, for correction of the deformity, together with transplantation of an autogenous graft from the right tibia. Operation showed that the fracture of the left tibia was ununited, the fragments being held by a thin layer of fibrous tissue without any evidence of callus formation. This tissue was removed, and section showed bone, cartilage and fibrous tissue, with no other remarkable microsopic changes. As union did not appear satisfactory, a further autogenous

Fig. 3.—Roentgenograms of the left leg, anteroposterior and lateral views.

graft, this time removed from the left ilium, was transplanted about two months later. Bony union with good callus formation was shown in a roentgenographic examination half a year later. However, the lower end of the left fibula showed more anterior curvature (fig. 3).

In October 1938, the patient was given a long leg brace, with the aid of which he was able to walk for a year, until it became too short. He then discarded the brace and said that he was able to walk with the help of a stick, until November 1940, when the left leg gradually became frail at the site of the old fracture. Roentgenologic examination on March 15, 1941 showed recurrence of the pseudarthrosis of the left tibia; there was union of the bone graft with the proximal fragment of the tibia, but not with the distal fragment. In addition, there was a new fracture of the left fibula just above the lateral malleolus. Some callus was seen about the fragments, but no union was evident, thus indicating pseudarthrosis. Pseudarthrosis of the right fibula also was present at the junction of its middle and lower thirds.

CLASSIFICATION

Henderson[4] and many other authors favored the classifications suggested by Gasne and Codivilla. To cite from Henderson, Gasne classified cases of the congenital type of pseudarthrosis into four subgroups: (1) cases in which distinct angulation is present at birth but with no fracture; (2) cases like those of the first group but with the development of pseudarthrosis after slight trauma, or after an operation for correction of the deformity; (3) cases in which pseudarthrosis is present at birth, and (4) cases in which the extremities appear normal at birth but, perhaps after slight trauma, a fracture occurs later, becoming pseudarthrosis. Codivilla, who was also cited by Henderson, on the other hand, classified congenital pseudarthrosis of the tibia into three subgroups: 1. The usual angular deformity, at the apex of which is a transparent or rarefied area, as shown on roentgenograms; the fibula is curved, although rarefaction is absent. 2. Typical pseudarthrosis—at the upper end of the lower fragment there often develops an articulating head, which fits into a sort of glenoid fossa formed by the upper fragment. 3. A great exaggeration of the condition as represented in groups 1 and 2, associated with loss of much bone in both tibia and fibula. Henderson, however, recognized only the first three subgroups of Gasne's classification as conforming with the congenital type.

ETIOLOGIC ASPECTS

Adult pseudarthrosis is generally believed to be caused by lack of proper immobilization after fracture; interposition of soft tissue structures between the fractured ends, or factors such as the presence of localized chronic infection, tumors, constitutional or nutritional diseases or neuropathic disturbances. Additional etiologic factors, as assembled by Blumenfeld, are: damage to the nutrient artery; inadequacy of blood minerals, such as calcium and phosphorus, or deficiency of vitamins C and D, and pathologic conditions of bone, such as carcinoma or osteitis deformans (Paget's disease). For the juvenile form, in addition to the expression of views somewhat similar to those given previously, Kelly added:

> If no definite cause other than imperfect fixation is present, then one can easily imagine that in children the fibroblasts are more active than the osteoblasts, and that with a fibrous union quickly effected and some motion allowed by loose fixation, the fibrous tissue quickly develops a bursalike quality and a pseudarthrosis is the result.

4. Henderson, M. S.: Pseudarthrosis of the Tibia in Children, J. Bone & Joint Surg. **7**:340-354 (April) 1925; Congenital Pseudarthrosis of the Tibia, ibid. **10**:483-491 (July) 1928.

Although histopathologic changes in the congenital type are somewhat similar to those of the adult type, views regarding the etiologic factors are much more divergent. The effect of amniotic pressure from cords or adhesions is considered important by some investigators; against this view is the one maintaining that the knee or foot should be more affected (Colonna [5]). Codivilla and Henderson attributed the condition to a lack of embryonal development and expressed the view that congenital interference with the development of the nutrient artery explains the lesion. This theory was also supported by Colonna. Inglis, on the other hand, observed no malformation of the nutrient artery (Scott [6]). Knaggs expressed belief in an early bone-destroying factor (Scott). Blood phosphorus, calcium and phosphatase concentrations and the Wassermann reaction throw no additional light. Henderson mentioned a case in which rickets was suspected. Scott cited an intrauterine metaplastic malacia, with the formation of osteoid tissue and pseudocysts, closely related to osteitis fibrosa cystica. Compere [7] mentioned that Stierlin, von Beust and Fragenheim were of the opinion that cystic disease of the bone is the underlying cause, but he added that Inglis and Camurati, on the other hand, discovered but little evidence of osteitis fibrosa cystica. The occurrence of pseudarthrosis in families with neurofibromatosis (von Recklinghausen's disease) was recorded by a few observers, including Ducroquet and Cottard [8] and Barber.[9] A congenital factor appeared to be present, as there were instances of the disease through three generations. However, most observers expressed the belief that congenital pseudarthrosis of the tibia is brought about by some modification in the blood supply (poorer vascularity of the lower half of the tibia) together with the gorilla-like stance of childhood, whereby the greatest stress is directed on the junction between the middle and the lower third of the tibia (Scott). All investigators commented on the fact that the general condition of the patient is usually good and emphasized that, whatever it may be, the cause must be local (Henderson).

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5. Colonna, P. C.: Congenital Pseudarthrosis of the Leg, J. A. M. A. **103**:2012-2016 (Dec. 29) 1934.

6. Scott, C. R.: Congenital Pseudarthrosis of the Tibia, Am. J. Roentgenol. **42**:104-109 (July) 1939.

7. Compere, E. L.: Localized Osteitis Fibrosa in the New-Born and Congenital Pseudarthrosis, J. Bone & Joint Surg. **18**:513-523 (April) 1936.

8. Ducroquet and Cottard: Pseudarthrose congénitale de jambe: Déformation osseuse de la neurofibromatosis, J. de chir. **53**:483-502 (April) 1939; abstracted, Internat. Abstr. Surg. **69**:373 (Oct.) 1939.

9. Barber, C. G.: Congenital Bowing and Pseudarthrosis of the Lower Leg: Manifestations of von Recklinghausen's Neurofibromatosis, Surg., Gynec. & Obst. **69**:618-626 (Nov.) 1939.

While reviewing published roentgenograms, I was struck by the similarity in appearance between some cases of congenital pseudarthrosis of the tibia and certain types of bone dystrophies and malacias. Particularly striking is the resemblance to fragilitas ossium, especially the form localized to one or two regions. A similar impression may be gained from simple inspection of cases of this disease showing a saber-like deformity of the leg. This idea of a possible relation between congenital pseudarthrosis of the tibia and fragilitas ossium had evidently been entertained by Kenwell (according to Colonna). Kenwell's patient presented distinct blueness of the scleras, but since autopsy showed no evidence of other fractures the diagnosis of fragilitas ossium was dropped. It is true that in fragilitas ossium there is usually prompt union of fractures, but occasional reports do indicate that healing may be delayed, either through improper immobilization or perhaps through an inherent tendency toward delayed healing. Thus, Key [10] reported a case of fragilitas ossium with nonunion of the left tibia in which healing occurred promptly after operation. Key also mentioned that Gutzeit had a case of nonhereditary fragilitas ossium with nonunion of the patella. According to Bell,[11] Aubineau reported a case of the disease showing multiple fractures of the femur with difficult consolidation necessitating operation. Bell also cited Burns's description of a family of 11 siblings of which 5 male members had fragilitas ossium. All 5 patients showed ununited fractures of one or both femurs occurring in later life; bone grafting was done several times on 2 patients, without effect, while another probably had fibrous union. Shugrue, Rockwood and Anderson [12] reported a case of fragilitas ossium in a youth aged 20, who had had ununited fractures of both elbows from the age of 15; the father of this patient had a fracture of the right leg which failed to unite, and the leg finally had to be amputated. Sisk [13] described a unique example of fragilitas ossium in twins, both of whom had ununited fractures of the femurs. Turner [14] came across 4 cases of fragilitas ossium in one family, 1 member of which, a boy aged 6 years, had an ununited fracture of the left femur. A case of ununited fracture of the left ulna in a patient with fragilitas ossium

10. Key, J. A.: Brittle Bones and Blue Sclera: Hereditary Hypoplasia of the Mesenchyme, Arch. Surg. **13**:523-667 (Oct.) 1926.

11. Bell, J.: Blue Sclerotics and Fragility of Bone in Hereditary Optic Atrophy, in The Treasury of Human Inheritance, London, Cambridge University Press, 1928, vol. 2, pt. 3, pp. 269-324.

12. Shugrue, J. J.; Rockwood, R., and Anderson, E. W.: Fragilitas Ossium and Deafness, Arch. Int. Med. **39**:98-108 (Jan.) 1927.

13. Sisk, J. N.: Fragilitas Ossium in Twins: Case Report, Wisconsin M. J. **30**:272-273 (April) 1931.

14. Turner, W. G.: Four Cases of Osteogenesis Imperfecta in One Family, Canad. M. A. J. **26**:659-662 (June) 1932.

was recorded by Goin.[15] Henderson[16] reported a case of the disease in a youth 18 years of age who showed nonunion of fractures in both femurs; operation on one side, using a graft derived from the mother's tibia, successfully brought about union.

Gambirassi[17] reported a case of osteogenesis imperfecta tarda in a woman aged 39, with ununited fracture of the left leg, which subsequently required operation. In the files of the roentgenographic department of the University of Michigan, also, I discovered a case of fragilitas ossium in a child who had multiple fractures, with persistent nonunion of a humeral fracture.[18] These examples suggest that delayed union, or persistent nonunion, of fractures in cases of fragilitas ossium is not so rare as is commonly thought and that occurrence of pseudarthrosis in this disease should also be expected. Thus, in addition to Kenwell's case mentioned previously, Smith[19] reported 2 cases of pseudarthrosis complicating fragilitas ossium. One case was that of a girl 8 months of age with pseudarthrosis of the left femur, while the other was of a girl 2 years of age with pseudarthrosis of the left tibia. Weber,[20] from pathologic examination of an infant with multiple fractures who died in early childhood, noted the presence of cartilage in a fracture of the right femur, thus indicating pseudarthrosis. Hansen[21] reported the occurrence of pseudojoints in the elbows of a girl 12 years of age with fragilitas ossium. Gambirassi recorded a case of fragilitas ossium in a 3½ year old boy who presented coarse knobbing of the right humerus resembling pseudarthrosis. Gambirassi further mentioned a case of Gamboa and Salvati, namely, that of a girl 4 years of age with multiple fractures, in which roentgenograms showed pseudarthrosis of both femurs. As an additional point to support this line of reasoning, one may cite the 2 cases of fragilitas ossium described by Smith[19] showing deformation of the tibia not unlike that seen in congenital pseudarthrosis of the tibia. The changes in the leg in these

15. Goin, L. S.: Idiopathic Osteopsathyrosis, Am. J. Cancer **17**:668-681 (March) 1933.

16. Henderson, M. S.: Clinical Use of Bone Craft in Fractures: Homogenous Bone Graft for Nonunion of Femur in Fragilitas Ossium, Proc. Staff Meet., Mayo Clin. **8**:259-263 (April 26) 1933.

17. Gambirassi, A. C.: Formas precoces y tardías de la enfermedad de Lobstein, Arch. argent. de pediat. **15**:517-553 (June) 1941.

18. Dr. Fred J. Hodges gave permission for the use of this case.

19. Smith, A. D.: Use of Homologous Bone Grafts in Cases of Osteogenesis Imperfecta, Arch. Surg. **34**:687-694 (April) 1937.

20. Weber, M.: Osteogenesis Imperfecta Congenita: A Study of Its Histopathogenesis, Arch. Path. **9**:984-1006 (May) 1930.

21. Hansen, A. E.: Influence of Viosterol and Parathyroid Extract on Mineral Metabolism in Osteogenesis Imperfecta, Am. J. Dis. Child. **50**:132-157 (July) 1935.

cases could reasonably be classified as instances of congenital pseudarthrosis of the tibia showing angulation at birth but with no evidence of fracture, i. e., conforming with group 1 of the classification of Gasne.

PATHOLOGIC CHANGES

Gross Appearance.—In a typical example of pseudarthrosis, there is deformity ranging from mild bowing to acute angulation of the tibia or fibula, or of both, at the site or level of the pseudarthrosis. Varying degrees of localized or generalized atrophy of the bone affected with pseudarthrosis, or at times even of unaffected bones, is usually present. Pseudarthrosis is stated to occur most frequently at the junction between the middle and the lower third of the tibia. Dillehunt and Le Cocq [22] reported a case in which the pseudarthrosis occurred at the upper end of the tibia; it seems that this case should be classified as one of the noncongenital type because of the absence of bone atrophy and deformity, the fracture in late infancy and the rapid healing after operation. Brailsford's case [23] showed pseudarthrosis occurring in the middle of the tibia. I have seen no pathologic report showing a distinct jointlike cavity filled with fluid in a case of pseudarthrosis of the congenital form.

Microscopic Appearance.—Colonna [5] reported the presence of centrally situated connective tissue, partly fibrous and partly fibroblastic, in the lower third of one or both bones of the leg. Inglis (cited by other authors, including Scott), from an investigation on 3 infants, reported osteoid tissue, poor vascularization and, in certain sections, frank hemorrhage with formation of pigment. He concluded that the centrally located connective tissue probably represented marrow which had once been normal and later became fibrotic, or that the medullary canal originally had been occupied by connective tissue which was mainly fibrous, normal marrow being inconspicuous or absent. In no section did he observe any indication of infection. There was, however, pronounced avascularization in the older infants, but no evidence of malformation of the nutrient artery. Of the cases of pseudarthrosis occurring with fragilitas ossium, Weber [20] observed cartilage in 1, while Smith [19] mentioned the presence of fibrous or soft osteoid tissue. Scott [6] presented a case showing changes similar to those of localized osteitis fibrosa cystica. According to him, the initial process is an intrauterine metaplastic malacia with the formation of osteoid tissue limited to the tibia and fibula. All fat may be absent, while the bone may show irregular foci coalescing into dense sclerotic masses or slowly

22. Dillehunt, R. B., and Le Cocq, J. F.: Pseudarthrosis of the Tibia in Young Children, J. A. M. A. **90**:1615-1617 (May 19) 1928.

23. Brailsford, J. F.: The Radiology of Bones and Joints, Baltimore, William Wood & Company, 1935, p. 125.

disintegrating into pseudocystic areas. These pseudocystic areas show a tendency to be cortical or subperiosteal; they are usually avascular but may enlarge, coalesce or disappear over varying periods of time. Any portion of the shaft may be involved at one time or another. Basseta (cited by Colonna [5]) described an early prefracture stage in a 14 week fetus in which blood clot, consisting of a net of fibrin and a few stellar connective tissue cells, was observed between the ends of the bone. The present case showed normal bone and soft tissue.

ROENTGENOLOGIC FEATURES

Roentgenologic study is indispensable both in the diagnosis and in the follow-up examinations. Moreover, the demonstration of atrophy and deformity unsuspected clinically cannot otherwise be made during life. Published roentgenograms reveal that a usual case of congenital pseudarthrosis will show varying degrees of atrophy and deformity of the shaft of the tibia or of the fibula, or of both, with the pseudarthrosis located in the lower half of the bone. A typical pseudarthrosis often appears as a well defined jointlike space between the fractured ends, the upper fragment usually being broader and cupped so as to accommodate the smooth, rounded lower fragment, or vice versa. If the accommodation is deep enough, there will then be a strong resemblance to the ball and socket type of articulation. The fractured ends may at times show extensive sclerosis with obliteration of the marrow cavity. In other instances, the pseudarthrosis may be represented by a fairly sharp transverse or oblique line of radiolucency, or it may be serrated, with small radiolucent areas suggestive of osteitis fibrosa cystica (Colonna) or of pseudocysts. Other variations, however, may occur. Instead of a well defined jointlike space, the fractured ends may be separated by a wide and irregular radiolucent area. The fractured ends may be narrowed, even to the extent of being sharp and spikelike. Varying degrees of overriding may be present. Bowing of bone, which may be gentle, or extreme and acute, occasionally up to 90 degrees or more, may occur. The direction of the bowing usually is anterolateral, but posterolateral or medial bowing may occur. Usually, both tibia and fibula show parallel curvatures, but sometimes their respective directions may diverge, as in the present case. Old healed fractures, partial or complete, can often be detected, and their presence may explain the deformity of a bone which does not show any evidence of pseudarthrosis. The degree of atrophy varies; it may also occur in a bone unaffected by pseudarthrosis, in the same or the opposite limb. The fibula usually shows more extensive atrophy than the tibia, appearing almost threadlike at times. Small or good-sized cystlike areas of radiolucency may be seen at the site of the pseudarthrosis or in other

parts of the bone. There may be varying degrees of osteoporosis, the most pronounced lesions showing homogeneous consistency; this may be due in part to disuse and in part to dystrophic or malacic factors. Occasionally, sclerosis may occur, with localized thickening of the cortex. Multiple dense transverse lines may be present in the diaphysial ends, as in Brailsford's case [23] and in the present case. Hardly any case shows remarkable changes in the epiphyses.

CLINICAL FEATURES

A typical case shows bowing or angular deformity of one or of both legs with fracture of one or more long bones, which show persistent mobility due to pseudarthrosis. Pain, slight or exquisite, may be localized at the site of the fracture. Physical examination may disclose atrophy of bone. The pseudarthrosis may occur at birth, in infancy or in later childhood. A statistical survey of cases which I believe conform with the congenital type of pseudarthrosis of the tibia, gathered from reports by Barber, Colonna, Hallock [24] and Henderson, Scott and McFarland,[25] including the present case, shows a sex incidence of 20 male patients to 15 female patients; that is, 58 per cent are males. It is of interest to note that in Blumenfeld's series of 135 cases of non-congenital pseudarthrosis of the long bones, male patients also predominated but with a slightly higher percentage, namely, 69.7. The general condition of the patient is usually good. These fractures are most refractory during infancy and childhood, showing a better tendency to heal only during adolescence. Operations performed before 6 to 8 years of age seem prone to end in failure. Repeated failures are not uncommon, and amputation was resorted to in a few desperate cases. The association of pseudarthrosis with neurofibromatosis (von Recklinghausen) was mentioned previously; in fact, Ducroquet and Cottard reported the constant association of three signs in many of their cases, namely, bowed tibias, café-au-lait spots on the skin and neurofibromatosis, with accompanying scoliosis.

TREATMENT

No special measures are necessary for the general care of the patient, since the condition as a whole, is usually good. In regard to the more conservative measures of dealing with the pseudarthrosis, Kelly stated that in instances in which fixation has been ineffective better

24. Hallock, H.: The Use of Multiple Small Bone Transplants in the Treatment of Pseudarthrosis of the Tibia of Congenital Origin or Following Ostectomy for the Correction of the Congenital Deformity, J. Bone & Joint Surg. **20**:648-660 (July) 1938.

25. McFarland, B.: Birth Fracture of the Tibia, Brit. J. Surg. **27**:706-712 (April) 1940.

immobilization should be tried, although there are a few cases of slow union which may respond favorably to the irritation and stimulation of slight motion and a little use, to tapotement or to Bier's passive hyperemia. Kelly continued that stimulation may also be effected by injecting a few drops of iodine or turpentine, or several drachms of blood drawn from the patient's arm, and that drilling the fragments may have a similar effect. However, operative intervention seems to be the method of choice; but, since the pseudarthrosis is notoriously refractory to operation performed before the patient is 6 to 8 years of age, the majority of authors advised deferring operation until adolescence, when the chance of healing improves. The statistics of most workers have shown that operative successes seldom exceed 50 per cent. Henderson recommended careful improvement of the general health, local physical therapy and a walking caliper splint as preliminaries to any operative procedure. He added that any deformity must be corrected either before or at the time of operation.

Henderson supplied a comprehensive account of the types of operations in mode: (1) the Italian method advocated by Reichel and practiced by Codivilla, consisting of an osteoperiosteal pedunculated graft swung over from the sound tibia to the area of pseudarthrosis; (2) bone grafting, either by the inlay method of Albee or by the massive method; (3) use of the osteoperiosteal graft (Delangière), either as a free graft from the opposite leg or as a dependent graft swung down from the upper fragment, and (4) shortening of the leg enough to get good side to side apposition and approximation of the fragments. Henderson himself advocated using a homologous graft derived from the mother's tibia. Massart [26] recommended Albee's operation, using a periosteal-osseous transplant taken from the maternal limb; if the tibia only is affected, it is necessary to break the curved fibula before removing the thick fibrous tissue which covers the surfaces and forms the capsule of the false joint. Smith excised the area of pseudarthrosis and used one or more onlay grafts from the tibia of the patient's mother. Hallock [24] was in favor of using multiple small bone transplants in a groove, as these seem to take better than massive grafts; he considered operation ineffective in the case of patients under 12 years of age. McFarland [25] reported successful operation in 2 cases with his "by-pass" graft, 1 patient having had multiple operations previously. He said:

> The . . . method consists in ignoring the zone of absorption and placing a strong bone-graft behind the tibia, implanting the graft into the back of the bone well above and below the site of non-union. It is a sort of 'bony by-pass' and carries the weight directly from the upper part of the bone to the lower.

26. Massart, R.: Traitement de la pseudarthrose congénitale du tibia, Bull. et mêm. Soc. d. chirurgiens de Paris **27**:78-81 (Feb. 1) 1935; abstracted, Edinburgh M. J. **42**:563, 1935.

He expressed the belief that with this method, surgical intervention has its place in childhood. After a review of various technics, Watson-Jones [27] voiced the opinion that his new method of double onlay grafts derived from the mother of the infant and screwed together with vitallium® screws will prove superior to preexisting procedures. Malkin [28] observed that the notoriously poor circulation of the lower third of the tibia, coupled with the strangulation of single grafts by scar tissue and the difficulty of adequate fixation, accounts for some of the failures in the treatment of congenital pseudarthrosis of the tibia.

Therefore, I advocate a combination of Brittain's method of cutting from the other tibia a massive tibial graft, with Boyd's plan of using twin grafts between which cancellous bone is packed, on the ground that the twin grafts form a protective scaffolding for the cancellous bone packed between them and a buttress against strangulation by scar tissue. This structure allows circulation to be developed and maintained and new bone to be formed, with subsequent healing of the fracture. Surgical treatment, although affording temporary alleviation, was unsuccessful in the present case.

As recent concepts of the treatment of fractures and of the use of bone grafts have a bearing on the problem of pseudarthrosis, a brief review will be of interest. For tibial defects, Davis [29] recently improved on the method originally suggested by Hahn by employing a one step substitution or reenforcement of the defective tibia with the fibula, with or without the addition of a sliding or inlay graft. It is now generally recognized that vitallium® screws are more effective than bone pegs in the fixation of grafts. Furthermore, in bone transplantation work, chips or struts derived from the iliac bone have been found superior to bone derived from other sources, as observed by several workers, including Dick [30] and Luckey and Adams.[31] The iliac bone stands injury better than any other bone, and its rate of recovery is rapid. McCarroll [32] recommended the use of small threaded wires in the fixation of bone grafts, after giving credit to Crego and Miller for popularizing the method.

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27. Watson-Jones, R.: Fractures and Joint Injuries, ed. 3, Edinburgh, E. & S. Livingstone, 1943.

28. Malkin, A. S.: Congenital Pseudarthrosis of the Tibia Treated by Twin Grafts, Proc. Roy. Soc. Med. **38**:71-74 (Dec.) 1944.

29. Davis, A. G.: Fibular Substitution for Tibial Defects, J. Bone & Joint Surg. **26**:229-237 (April) 1944.

30. Dick, I. L.: Iliac Bone Transplantation: Preliminary Observations, J. Bone & Joint Surg. **28**:1-18 (Jan.) 1946.

31. Luckey, C. A., and Adams, C. O.: The Use of Iliac Bone in Bone-Grafting and Arthrodesis, J. Bone & Joint Surg. **28**:521-534 (July) 1946.

32. McCarroll, H. R.: Use of Small Threaded Wires in the Treatment of Fractures: III. Their Use in the Fixation of Bone Grafts, Arch. Surg. **54**:171-182 (Feb.) 1947.

COMMENT

Congenital pseudarthrosis of the tibia is a rare disease. Like many other bone anomalies, there is still confusion regarding definition, classification and, particularly, etiologic factors. With regard to definition, one should, strictly speaking, apply the term pseudarthrosis only to those cases which show the development of a jointlike space containing fluid. "The American Illustrated Medical Dictionary" [33] defines pseudarthrosis as: "A false joint, as that sometimes seen following a fracture." Treves [34] stated that pseudarthrosis is a general term used to indicate the permanent presence, after a fracture, of abnormal mobility in a bone due to (1) fibrous union, (2) nonunion or (3) false joint. Keen and White [35] stated that when abnormal mobility has not ceased after the normal lapse of time the condition is described as delayed union; if this condition persists after some additional weeks, it is termed pseudarthrosis, or failure of union, or ununited fracture. Anatomically, two distinct varieties exist: in one, the fragments are more or less closely bound together by solid bands of fibrous tissue, sometimes enclosing nodules of bone; in the other, similar fibrous bands enclose a central cavity containing a viscid, synovia-like fluid, into which the ends of the fragments may project, or these ends may be smooth or eburnated, or even covered with hyaline cartilage, as in a complete joint. However, under the heading of "defective formation of callus," Eisendrath [36] stated that the term pseudarthrosis should be applied only to those cases in which a false joint is formed at the seat of the fracture.

Thus, one can see how varied are the interpretations of the term pseudarthrosis. It is generally conceded that cases showing joint formation in the usual sense of the word, that is, with a cavity containing synovia-like fluid and lined with either a fibrous wall or with a shiny, secreting membrane, are seldom encountered. The majority of cases show mainly a fibrous partition, at times with fibrocystic changes. For want of a better term, however, and through common usage, such cases usually have been named pseudarthrosis. Apparently, this terminology is justified technically, because in anatomic nomenclature fibrous union (syndesmosis) is also classified under the heading of joints.

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33. Dorland, W. A. N., and Miller, E. C. L.: The American Illustrated Medical Dictionary, ed. 20, Philadelphia, W. B. Saunders Company, 1944.

34. Treves, W.: System of Surgery, Philadelphia, Lea Bros., 1895, p. 791.

35. Keen, W. W., and White, J. W.: An American Text-Book of Surgery, Philadelphia, W. B. Saunders Company, 1899, p. 300.

36. Eisendrath, D. N.: Section on Orthopedics, in Keen, W. W., and White, J. W.: An American Text-Book of Surgery, Philadelphia, W. B. Saunders Company, 1911, vol. 2, p. 107.

The commonly accepted classifications of congenital pseudarthrosis are based on those of Gasne and of Codivilla. Strictly speaking, cases in which there is no deformity at birth but in which pseudarthrosis subsequently develops after trauma (group 4 of Gasne) should not be considered as belonging to the congenital type. Henderson seemed justified, therefore, in accepting only Gasne's first three groups as conforming to the congenital type. As for cases in which deformity of bone is present at birth but in which there is no evidence of pseudarthrosis (group 1 of Gasne, and possibly group 1 of Codivilla), it is perhaps preferable that this type be regarded as a different entity until pseudarthrosis occurs, if it does. Attention, too, has been called to the similarity in roentgenologic appearance of this type to that of fragilitas ossium localized in the leg.

Although many authors seem to accept the view that congenital pseudarthrosis of the tibia is a single entity, its etiologic aspects appear to be much more complex. The association of congenital pseudarthrosis of the tibia with osteitis fibrosa cystica or with bone cysts has been mentioned by some authors. Recently, several cases of congenital pseudarthrosis were reported which showed a close relation with neurofibromatosis (von Recklinghausen). A hereditary factor is present. Ducroquet observed so many cases of this type that he stated the belief that in isolated instances in which neurofibromatosis is not definitely mentioned it would be possible, to find manifestations of von Recklinghausen's disease within the third or fourth generations (Barber [9]).

There is a remarkable similarity between the roentgenologic features of congenital pseudarthrosis of the tibia and those in some cases of fragilitas ossium, particularly of the form localized to the leg. Furthermore, in some cases of congenital pseudarthrosis of the tibia there is involvement not only of one bone but of many bones, including the fibula. It also has been demonstrated that delayed union, and even persistent nonunion, of fractures can sometimes occur in fragilitas ossium, and that this may occasionally end in pseudarthrosis. The resemblance between congenital pseudarthrosis of the tibia and fragilitas ossium would have been more complete were it not for the fact that in hardly any case of congenital pseudarthrosis of the tibia so far reported were there the hereditary qualities so characteristic of fragilitas ossium: blue scleras, deafness and hyperlaxity of ligaments, among other signs. Kenwell's case of pseudarthrosis with blue scleras, may be cited as an occasional exception. Perhaps too much attention was focused on the pseudarthrosis in the past, to the exclusion of other relevant observations and data. As matters stand, it cannot be denied that there are many features in common to congenital pseudarthrosis of the tibia and to fragilitas ossium localized to the leg. However, when one recalls that even in some cases of fragilitas ossium nonhereditary

features are present, the evidence suggesting that congenital pseudarthrosis of the tibia is in all probability a variant of the fragilitas ossium group seems stronger than ever.

The treatment of congenital pseudarthrosis of the tibia is beset with difficulties, apparently because of the inferior quality of the atrophic and dystrophic bone tissue present. Operative successes were reported in less than half of all cases, and failures seem to be the rule when children of 8 years of age or under are treated surgically. For this reason, many surgeons advise deferring operation until adolescence. Many types of operations were described in the past. It would seem that with the more modern technics, in combination with other recent advances in orthopedic surgery, operations performed even in early childhood should offer a better chance of firm bony union than was possible in the past.

SUMMARY

A case of so-called cogenital pseudarthrosis of the tibia in a boy of French origin is reported. Roentgenograms showed pronounced atrophy, with deformity of the involved bones of both legs, resulting in a condition not unlike that seen in fragilitas ossium. Repeated bone graftings were unsuccessful in effecting firm union.

A comprehensive review of the various aspects of congenital pseudarthrosis of the tibia is included, particular stress being laid on etiologic factors and surgical treatment. Because of the many points of similarity between congenital pseudarthrosis of the tibia and the form of fragilitas ossium localized to the leg, it is concluded that congenital pseudarthrosis of the tibia is in all likelihood a variant of fragilitas ossium.

Dr. C. K. Hsieh, Dr. C. J. Hsu and Dr. K. P. Chang aided in the preparation of this paper.

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OFFICE MANAGEMENT OF THE ALLERGIC CHILD

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IN A discussion of this subject it is pertinent to point out the essential differences between the allergist who is a pediatrician and the allergist who is an internist. Many of the allergists who are internists, and this includes younger as well as older physicians, feel that there is no such thing, properly speaking, as pediatric allergy. They point with pride to the large number of children in their practices, particularly those who flock in all day Saturday for their injections of pollen or dust extracts and vaccine. However, a close examination of the makeup of the majority of such practices, as concerns pediatrics, reveals that most of these patients are afflicted with typical pollinosis or typical bronchial asthma, the treatment of which is not essentially different in children, at least beyond the age of 2 or 3 years, from that in adults. In fact, the internist-allergist can generally treat these patients more successfully than their counterparts in adult life because they present fewer complications, and at this age the tendency to recover spontaneously or to "outgrow" the condition is greater than in any other period of life. In the practice of the internist-allergist, also, are usually found very few infants and children with the eczematoid dermatoses and not nearly as many patients with recurrent conditions of the upper respiratory tract, disorders which form a significant portion of the practice of the pediatric allergist.

It is further my feeling that the field *par excellence* of the pediatric allergist is the working out of the problems of prophylaxis in allergic disease. For this reason, the pediatric allergist should not only accept as patients children with clinical allergic manifestations but also welcome for routine pediatric care newborn infants and other children without evident allergies from families in which the parents or siblings suffer from allergic disease. This is necessary if he is to study allergic disease from its very beginnings. Thus, it is obvious that the pediatric allergist must be an exceedingly well trained pediatrician and may never properly devote himself exclusively to allergy, as has been the case for

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This paper was presented at the Southwest Allergy Forum, Shreveport, La., April 1, 1947.

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years with many internists. For the fulfilment of this purpose the cooperation of the obstetrician must be secured, and in my own personal experience this has not been difficult. The pediatric allergist, also, should not hesitate to act as a consultant in adult allergy when requested to do so by the patient's physician. These experiences are highly stimulating and instructive.

It is essential that the pediatric allergist be thoroughly familiar with infant feeding, environmental control, the peculiarities of the skin of infants and the special technics employed in the testing of infants and young children. He should know, as has been mentioned, as much as possible concerning the prophylaxis of allergic disease. This should include attempted prevention of the development of psychosomatic disorders in children with chronic disabling allergies, especially bronchial asthma at any age and chronic atopic dermatitis in adolescence. The internist who is also an allergist must particularly consider allergy in its relationship to the degenerative, neoplastic and psychosomatic diseases of adult life.

The subject of this discussion is broad, and, since most of the management of the allergic patient is directed in the office of the allergist, whether pediatrician or internist, the topic could embrace practically the entire field of clinical allergy. However, the discussion will be largely limited to what is considered to be the special field of the pediatric allergist; so, generally speaking, this presentation will concern the infant and child up to the age of 2 or 3 years.

TAKING THE HISTORY

The essential components of any case study are the history, the physical examination and the special tests pertinent to the condition being studied. In allergy, and this holds true for children as well as for adults, the most important of these three is the history. Details of history taking with particular reference to adults were thoroughly discussed by Rackemann [1] and by Swineford and Weaver.[2] For children it is my custom to take a detailed history and make a complete physical examination at the first visit. This must be done with great care and may require an hour to an hour and a half. It is always requested that some one accompany the parent and child to the office so that the parent may be interrogated alone while the child, supervised by the parent's companion, is amusing himself in the waiting room which is particularly designed for that purpose. It is practically impossible to

1. Rackemann, F. M.: History Taking in Allergic Diseases, J. A. M. A. **106**:976 (March 21) 1936.

2. Swineford, O., Jr., and Weaver, W. M.: History Taking in Allergy, Ann. Int. Med. **20**:293, 1944.

take an accurate history with the child in the same room, as the presence of the child distracts both the parent and the physician. The parent, for purposes of this discussion, refers to the mother, since the father, as in most history taking in pediatric practice, usually is totally unfamiliar with the pertinent facts.

The natural history of the onset and course of allergic disease in infancy and childhood assumes a rather definite, though by no means invariable, pattern, which I shall try to follow through this discussion. It is always well to start with the chief complaints, as they are uppermost in the parent's mind. A discussion of them is in no way different from that commonly employed with adults. In the taking of the past history, however, there are some essential differences. The allergist should know, for example, whether the mother had any particular food cravings during pregnancy, as occasionally overindulgence in any one particular food may sensitize the infant to that food. Such incidents, described by Ratner,[3] although rare, are interesting and illuminate the problem of allergy in childhood at least to the extent that it should be a routine measure to warn the mother of a potentially allergic child to eat a wide variety of food during pregnancy and not concentrate, as pregnant women occasionally do, on any particular single item.

Whether or not the child is breast fed is also a matter of importance because almost any food or drug may pass through the breast milk sufficiently unchanged and in sufficient quantities to cause allergic manifestations in the infant. Whether or not clinical sensitivity to human breast milk occurs is problematic. I recently treated a breast-fed infant with severe atopic dermatitis who reacted to many foods, including cow's milk, goat's milk and human breast milk. Purely as an experimental measure, because of the importance of the reaction to the human breast milk, I allowed breast feeding to continue and removed from the mother's diet those other foods, to which procedure the child reacted with startling and satisfactory improvement within a week. At the end of this period the child still gave a positive reaction on scratch test to human breast milk, thus indicating that in this instance the reaction was not of clinical significance. If the child is not breast fed, it is important to know what formulas he was fed and the dates and types of subsequent additions of various foods and vitamin preparations. If possible, these should be correlated with the child's allergic manifestations. Any infant who has had repeated changes in formulas because of gastrointestinal discomfort, vomiting, diarrhea or failure to gain properly is commonly an allergic infant.

3. Ratner, B.: A Possible Causal Factor of Food Allergy in Certain Infants, Am. J. Dis. Child. **36**:277 (Aug.) 1928. Ratner, B., and Greenburgh, J. E.: Congenital Protein Hypersensitiveness, J. Allergy **3**:149, 1931.

Urticaria.—The first clinical manifestation of allergy in the newborn human being is urticaria. This may occur even during the first day of life and is manifested by transient rashes, usually with only small wheals and larger flares. It is often unnoticed and rarely commented on except by the student nurse on the outlook for impetigo. I have never known urticaria during the newborn period to be a troublesome problem and no mother has ever mentioned this in giving a history. The urticarious rash usually disappears within a few days and probably represents in some way a reaction to the immunologic processes going on as the child adapts himself to the extrauterine environment.

Colic.—Colic, or gastroenterospasm, is the first clinical manifestation of allergy in the newborn human being of which the parent may complain. Usually, this starts during the first weeks of life and terminates, regardless of therapy, by the time the infant is 3 months of age. In other words, it occurs when the gastrointestinal tract is introduced to foreign proteins, either cow's milk or a variety of others which reach the infant in the mother's breast milk. Not all colic is of allergic origin, but the severer cases often are, and in proportion as the child suffers from colic so may subsequent manifestations of allergy appear in later infancy and childhood. Without going into any great detail, it may be said that the evidence of the allergic origin of colic may be divided into two classes: (1) presumptive and (2) specific. The presumptive evidence is as follows:

1. There is a definite incubation period of ten days to three weeks after birth before colic develops.

2. During the first weeks of life transient positive reactions to cutaneous tests occur which disappear as the child becomes accustomed to the new foods.[4]

3. Transient precipitins also occur in the blood stream to these allergens during the same period.[5]

4. Transient eosinophilia appears as new foods are introduced and disappears as the child becomes accustomed to these foods.[6]

5. Infants who have had colic have eczema more frequently than infants who did not have colic.[7]

The specific evidence that colic is due to allergy is its response to changes in diet. For example, the worst colics will often clear up

4. DuBois, R. O.; Schloss, O. M., and Anderson, A. F.: The Development of Cutaneous Hypersensitiveness Following Intestinal Absorption of Antigenic Protein, Proc. Soc. Exper. Biol. & Med. **23**:176, 1925.

5. Schloss, O. M., and Myers, C.: The Intestinal Absorption of Antigenic Protein, Proc. Soc. Exper. Biol. & Med. **23**:180, 1925.

6. Berger, H. C.: Eosinophilia Occurring in Infants Following the Ingestion of a Foreign Protein, Arch. Pediat. **33**:42, 1916.

7. White, P. J.: The Relation Between Colic and Eczema in Early Infancy, Am. J. Dis. Child. **38**:935 (Nov.) 1929.

when the formula is modified. If the child is given pasteurized milk, he may do better when he is fed an evaporated milk formula; if he is fed evaporated milk, he may do better when given some other type of formula. If the child is being given such a preparation and he has colic, it is highly probable that he is sensitive to the casein of the milk, as well as the lactalbumin, and therefore an entirely different type of milk must be used, since the casein of all mammalian milks is practically identical in composition. For substitute therapy, soybean milk is most commonly employed and is highly satisfactory. In those infants that do not respond to soybean milk, an equally good or even superior substitute is an artificial milk whose protein basis is a finely strained meat. These meats are now commercially available, so that this formula, which was first devised by Rowe,[8] can be easily put to practical use.[9]

Before leaving this subject, I should like to say a few words more about the "incubation period" of colic. If an animal is given an injection of a foreign protein, in the classic case he becomes sensitive to that protein and will react with anaphylactic shock from its reinjection at the end of a given period, usually seven to ten days. Something analogous occurs in the child when the foreign protein, milk, is absorbed by the gastrointestinal tract. I refer particularly to cow's milk, as this is the foreign protein most usually encountered by the newborn infant. Cow's milk is so commonly used in the feeding of infants that one often forgets that it is not a natural food for a newborn infant. The only natural food for the newborn infant or the infant during the first few months of life is human breast milk. After thousands of years of domestication, the cow, who rightly deserves the title of foster mother of the human race, still makes milk which is designed primarily for calves and not for human beings. The process of absorption of cow's milk in the gastrointestinal tract leads to a longer latent period than occurs in experimental animals when a foreign protein is injected, so that the incubation period of colic is ten days to three weeks. This leads to a curious phenomenon which is often not appreciated by the pediatrician. It is about this time that the child leaves the hospital with his mother for home. She then calls her pediatrician, and he usually feels that he can improve on the formula on which the child left the hospital. The formula is changed, and the colic may develop shortly

8. Rowe, A. H.: Elimination Diets and the Patient's Allergies: A Handbook of Allergy, Philadelphia, Lea & Febiger, 1941, p. 200.

9. Glaser, J.: The Use of Strained Meats as the Protein Basis of Milk Substitutes in the Treatment of Milk Allergy, J. Allergy **15**:283, 1944. Stuart, G. J.: A Simple Method for Preparing Strained Meat Formulas, ibid. **16**:253, 1945.

thereafter. Because the formula was changed by the pediatrician, the mother blames him for the child's colic and often turns to some other pediatrician for relief. The pediatrician who is familiar with this phenomenon will, if the child is doing well, not change the obstetrician's formula but allow the colic to develop, if it is going to, while the child is on that formula. Then he may make whatever changes he feels advisable. Colic does occur in the breast-fed infant, as well as in the bottle-fed infant, or even the infant fed exclusively on soybean milk from the day of birth, but time does not permit discussion of this interesting phenomenon.

While I am on the subject of gastrointestinal allergy in early infancy, it may be stated that the evidence is that pylorospasm and, therefore, presumably hypertrophic pyloric stenosis are probably on an allergic basis.[10] If such is the case, it is perhaps reasonable to conjecture that other diseases of infancy which may be secondary to spasm of smooth muscle sphincters, as hydroureter and congenital megacolon, may also be on an allergic basis. Evidence of this is, however, lacking.

Other Conditions.—In continuing the history taking, one also asks about croup. By this is meant typical spasmodic croup usually unaccompanied by fever in which the child awakens suddenly from sleep with a typical barking cough. The child is better during the daytime but is worse at night, and this condition persists for three or four days. Whether or not spasmodic croup is an allergic disease is doubtful. Personally, I think that it is probably due to some type of infection. However, a thorough study of this condition from the standpoint of allergy has not yet been presented.

One should further ask concerning the same diseases one would inquire about if the patient were an adult, as asthma, perennial allergic rhinitis, urticaria and perhaps others. Migraine rarely occurs in childhood, but it is well to ask whether the child has headaches. It is amazing that a child even 2 or 3 years of age may at times be able to indicate to the mother that he does suffer from headaches. Headaches, in children, particularly when accompanied with abdominal pain, are frequently the forerunners of migraine in older childhood and adult life, but in childhood the abdominal component is much more prominent than the cephalic.

The family history is interesting but not of great importance. Allergists practically universally agree that the more allergy in the ascendants, the more there will be in the descendants. In pediatrics one is somewhat handicapped because not infrequently, although the

10. Balyeat, R. M., and Pounders, C. M.: Pylorospasm Due to Allergy Simulating Infantile Pyloric Stenosis, South. M. J. **26**:436, 1933. Cohen, M. B., and Breitbart, J.: Infantile Pyloric Obstruction: Preliminary Report of Its Allergic Nature, Am. J. Dis. Child. **38**:741 (Oct.) 1929.

parents of the allergic child are potentially allergic, their manifestations may not develop until years after allergic signs appear in one of their children.

The other parts of the history about which one inquires are essentially the same as in adults. One can, however, inject a little propaganda into the history taking. For example, when one asks whether the child sleeps on a pillow, the parent can be advised, if the child does not yet have one, that the best pillow she can buy for him is one of sponge rubber or glass fiber, and if a mattress is needed one of sponge rubber is preferable. In the same way when asking about animal pets, if the family has none, one may say that since the child is allergic he will be much better off if no animal pets with fur or feathers are ever acquired. If such pets are kept, the parent should be instructed that in event the animals die, they should not be replaced. When asking about ozite® floor pads, which are made of hog and cattle hair, one can interject the remark that if such pads are used no more should be purchased but instead rubber pads should be employed.

Food dislikes in allergic children are perhaps of some importance. They occasionally indicate a subconscious defense reaction on the part of the child against a particular food, but this does not happen often enough so that it can be depended on. The child's dislikes are particularly significant when directed against foods which most children commonly like, as egg, milk or orange.

With children, as with adults, one also inquires regarding drug disagreements. Fortunately for the pediatrician, these are much less common in children than in adults. The commonest idiosyncrasy is to atropine and next to the barbiturates, which are excitants to many children rather than sedatives. Sensitivity to acetylsalicylic acid is rarely encountered, and I have never seen it in the severe fulminating form in which it may occur in adults. As a matter of routine, one should also inquire whether the child can tolerate the sulfonamide drugs and penicillin.

Regarding operations, the one which the child has most usually had is removal of the tonsils and adenoids. If the tonsils and adenoids or either have been removed more than once and one is sure that the operation was done in the first place by a capable physician, it is practically pathognomonic in my experience of an allergic child.

PHYSICAL EXAMINATION

With completion of the history taking, the highlights of which have been indicated, the next step is the complete physical examination. In the case of cutaneous diseases, it is desirable to be sure, if possible, whether or not the condition is of allergic origin. If there is any

doubt, the child should be referred to a dermatologist who should decide the question. If this is done, the pediatric allergist will not then be accused of subjecting to an allergic study patients with such conditions as scabies, pediculosis, psoriasis, lichen and perhaps other diseases.

While the diagnosis of allergic cutaneous conditions can usually be made without difficulty, errors may occur. In this connection the following case reports are of interest:

CASE 1.—This boy was 5 years old when first seen because of "eczema." The lesion had been present on the penis and surrounding area almost since birth. The pediatrician had stated that because the child would outgrow the eczema by the time he was 5 years old the mother should do nothing about it. However, at 4½ years of age, the condition appeared worse, if anything, and the mother was concerned about the child's not living up to her pediatrician's time table. There was, in this particular case, nothing in the child's personal history or in the family history to suggest allergic disease, and on inspection the condition proved to be psoriasis.

CASE 2.—This case is of even greater interest. The boy was 5 years old when first seen and had been under the care of the leading pediatrician in a large eastern city. When he was about 2 years of age, a dermatitis had appeared on his buttocks which was diagnosed as "eczema." Local treatment proved unavailing, but whenever the child was taken to the sea shore, where the family spent its summer vacation, the skin healed up nicely, thus attesting to the marvelous virtues of sea air and confirming the common observation that eczema is usually less troublesome in the summer than in the winter. The mother was told that the child would outgrow the eczema and that it was not necessary to have the child studied by an allergist. In this family also were two physicians (neither of whom was a pediatrician, allergist or dermatologist) who told the mother that she should stay away from the allergist since he would only subject the child to innumerable tests, next to impossible diets and other useless procedures which would be of considerable expense to the family without yielding any solution to the problem.

However, the condition became so bad that the mother finally brought the child in. The diagnosis of toilet-seat dermatitis was made on inspection without the necessity of doing cutaneous tests and the other procedures the mother had been warned against. As soon as the mother heard the words, "toilet-seat dermatitis," she snapped her fingers and said, "Why, I should have thought of that myself. Every time I put him on the toilet he rubs himself around against the seat and scratches himself."

For the purpose of recording the nature and extent of the cutaneous lesions, rubber stamps applied to the physical examination sheet are helpful. Two sets of stamps are used, one conforming to the configuration of the infant and the other to that of the older child. These were first described by me[11] a number of years ago. Stoesser[12] also employed somewhat similar figures on his record sheets.

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11. Glaser, J.: Anatomical Stamps for Depicting Dermatitis in Infants and Children, Letters of Internat. Corres. Club Allergy, 1943.

12. Stoesser, A. V.: Clinical Evaluation of Soy Bean Food in Eczema of the Child, Ann. Allergy **2**:404, 1945.

The pediatrician is occasionally urged to make a hard and fast diagnosis between seborrheic and atopic dermatitis. This may be done in some cases. However, oftentimes children are seen with apparently typical seborrheic dermatitis which, in the course of weeks or months, develops into typical atopic dermatitis. There is obviously some relationship between the two diseases, the nature of which is unknown. Simon [13] extracted a material from the scales of patients with seborrheic dermatitis for which reagins may be demonstrated in patients with atopic dermatitis. The practical point involved is that if the cutaneous lesions appear to be more seborrheic than atopic in nature a thorough trial should be given with topical applications before subjecting the patient to a complete allergic study.

The next allergic condition which commonly develops chronologically is the recurrent disorder of the upper respiratory tract. The diagnosis of this condition is quite easy if it is only kept in mind. The mother often gives the diagnosis with her chief complaint, "My child gets one cold after another." The differential diagnosis of this condition was thoroughly described by Cohen and Rudolph,[14] and it is greatly to their credit that practically nothing has been added to this since their publication on this subject in 1931. The allergic condition of the upper respiratory tract is recurrent. There are often mild symptoms between attacks. Usually a definite relationship to heredity is present. The condition is not contagious. It is not related to exposure to another case, and constitutional symptoms are slight. Foods and inhaled substances are often traced as causes. Itching and wheezing are common, and other allergic conditions are usually present or have occurred in the past. The opposite of these statements is true in the typical case of the infectious coryza.

On physical examination the nose often shows that the visible mucous membranes are pale, glistening and edematous in contrast to the hyperemic mucous membranes of the common cold. The discharge is thin and watery. Practically pathognomonic in the allergic respiratory condition is the demonstration of eosinophils in the mucous secretion of the nose. This is an important diagnostic procedure because if eosinophils are observed in significant numbers, the burden of proof rests with the physician who states that the child does not have allergic disease. Experience with direct smears of the nose of young children was not uniformly successful, especially when the secretion was scanty, until it was discovered that continuous direct

13. Simon, F. A.: Atopic Dermatitis in Infants, Children, and Adults, with Special Reference to the Role of Inhalants and Dander, J. Allergy **18**:186, 1947.

14. Cohen, M. B., and Rudolph, J. A.: Allergic and Infectious Conditions of Upper Respiratory Tract in Children: Differential Diagnosis, J. A. M. A. **97**:980 (Oct. 3) 1931.

contact of the swab with the mucous membrane for at least one minute would almost always result in positive smears in the case of an allergic mucous membrane. Infants and young children will not tolerate the presence of tightly wound cotton, even when not attached to a wire or toothpick, in their nasal passages for even a minute without crying. The tears passing through the nasolacrimal duct into the nasal cavity wash the swabs free of cells. However, on adaptation of the postnasal flexible wire swab of Bradford and Slavin[15] to this test, it is relatively simple to obtain good smears. These swabs, which consist merely of a cotton tip thinly, tightly and evenly wound around strands of flexible copper wire, were originally devised for taking postnasal cultures for detection of the presence of pertussis bacilli. When adapted for the purpose of demonstrating eosinophils, while the child is held firmly on his back the swab is inserted through a nostril until its tip rests against the posterior wall of the nasopharynx. The child is then turned over on his abdomen for a minute so that the tears will not flow back against the swab. It is then removed and a smear made which is stained by Hansel's method.[16] A less satisfactory method is to close the openings of the nasolacrimal ducts with the finger tips while the child is forcibly restrained and a nasal swab inserted.

Perennial Allergic Rhinitis.—Perennial allergic rhinitis is a condition which is common in young children but usually takes a milder form than in adults. It commonly develops about the age of 2 or 3 years concurrently with or independently of the recurrent disorders of the upper respiratory tract. It almost invariably accompanies bronchial asthma in the very young. Perennial allergic rhinitis is an exceedingly difficult and stubborn disease to treat. In most instances, as in the case of the recurrent infection of the upper respiratory tract, the parent will not cooperate in the study until the child's tonsils and adenoids have been removed. It is, therefore, best to refer these children to a laryngologist for his opinion. Because lymphoid hyperplasia is typical of these children, the removal of the tonsils and adenoids is often advised. Occasionally this will give some relief because at times adenoids do cause serious nasal obstruction, whether the patient is allergic or not. With the tonsils and adenoids removed, if the child's symptoms continue, the parent has little recourse but to submit the child to an allergic study. Often the results of this are disappointing, just as in the case of adults. However, by the proper use of nose drops and occasionally by the use of the so-called antihistaminic drugs, the condition may be kept under control. It is important in these

15. Bradford, W. L., and Slavin, B.: Nasopharyngeal Cultures in Pertussis, Proc. Soc. Exper. Biol. & Med. **43**:590, 1940.

16. Hansel, F. K.: Allergy of the Upper and Lower Respiratory Tracts in Children, Ann. Otol., Rhin. & Laryng. **49**:579, 1940.

children, regardless of the results of cutaneous tests, to observe allergic cleanliness, i. e., proper environmental control.

Pollinosis.—At about the same age perennial allergic rhinitis develops the child may also have pollinosis. The question as to the age at which one should begin the specific treatment of pollinosis is somewhat controversial. The consensus is that treatments should be started as soon as a positive diagnosis has been established, regardless of the age of the patient. There is no evidence that properly administered pollen therapy can increase the child's sensitivity to pollen. As a practical consideration, it should be explained to the parent that in the case of a mild pollinosis not a great deal of improvement may be expected, since as a rule the worse the pollinosis the more striking is the improvement on specific therapy. The object in treating the less severe cases is to do what one can to prevent the progression of the condition and its complications and sequelae, particularly asthma. If the child exhibits only slight symptoms in an unusually severe pollen season, it may be justifiable to treat the pollinosis only symptomatically, in the hope that the condition in successive seasons may be less severe. Specific therapy may be unnecessary or delayed until the child is older and treatments are less disagreeable both to the child and to the parent. The antihistaminic drugs will be particularly useful here, at least until it is determined whether or not the patient with pollinosis, while getting relief from these drugs, will tend regardless of their use to show development of bronchial asthma later. Pollinosis accompanied with pollen asthma is, however, an absolute indication for starting treatment at any age.

Bronchial Asthma.—The differential diagnosis of bronchial asthma at any age is not commonly attended with great difficulty. It must always be remembered that this diagnosis is based on clinical and not laboratory findings and that the patient should never be referred to an allergist for cutaneous testing "to see whether he has bronchial asthma." While in most instances the diagnosis may be made with accuracy from the history alone, yet it cannot be absolutely established unless the patient is examined during an attack.

The question of differential diagnosis of bronchial asthma probably arises oftener in infancy and childhood than in adult life for the reason that young children are subject to congenital stridors which cause wheezing respirations. Another factor is that infants and children may at times aspirate foreign bodies into their air passages without the knowledge of their parents. This may also cause wheezing and at times lead to a confusion in diagnosis.

In most of the standard textbooks bronchial asthma is defined as a paroxysmal form of dyspnea accompanied with wheezing. A

definition of this nature is highly inaccurate because there are many forms of wheezing which are not due to bronchial asthma. A suggested definition for bronchial asthma is as follows: Bronchial asthma[17] is a form of obstructive emphysema of allergic origin, involving both lungs throughout, characterized by paroxysmal attacks of dyspnea, chiefly expiratory, accompanied with wheezing heard on auscultation of the chest and typically relieved, at least in the early stages of an attack, by sympathomimetic drugs. The pathologic physiologic changes consist of edema, increased secretion of the mucous glands, spasm of smooth muscle and usually a local tissue and fluid eosinophilia.

This definition emphasizes the important fact that bronchial asthma is only one form of obstructive emphysema. It is, however, the commonest form. If this fact is kept in mind, the use of the confusing terms, "nonallergic asthma" or "para-asthma," as employed by Peshkin,[18] may be avoided. All so-called nonallergic asthmas are other forms of obstructive emphysema and should be so designated.

In my own experience the majority of infants referred under the age of 1 year because of bronchial asthma do not have this disease. Often it will be noted that the child lies on the examining table wheezing loudly. However, it will often be noted that in such instances the dyspnea is inspiratory rather than expiratory. This almost immediately rules out bronchial asthma, although in early infancy the dyspnea is not necessarily expiratory in character. It may resemble an ordinary dyspnea.[19] It is, however, difficult to time the respirations accurately in a dyspneic infant; the picture is further confused by the fact that the chest is small and round and sounds are easily transmitted from different parts. However, I have the impression that even in asthma at this age expiratory dyspnea is commoner than inspiratory, and, if this is not true, the diagnosis must be more carefully questioned than otherwise.

Foreign Body in the Bronchus.—Some of the most tragic mistakes in the differential diagnosis of bronchial asthma are made because the physician does not realize that the symptoms and physical signs of asthma may be produced to an exceedingly misleading extent by the presence of a foreign body in the bronchus. This is especially true in infancy and childhood because these patients appear at times to exercise almost diabolic ingenuity in getting unsuspected foreign bodies into the bronchial tree. The diagnosis may almost always be

17. Glaser, J.: Differential Diagnosis of Bronchial Asthma in Infancy and Childhood, Ann. Allergy **4**:409, 1946.

18. Peshkin, M. M.: Asthma in Children: Etiology, Am. J. Dis. Child. **31**:763 (June) 1926.

19. Kahn, I. S.: Essential Differences in Chronic Pollen Hay Fever and Asthma in Children and in Adults, J. Lab. & Clin. Med. **12**:1197, 1927.

made by roentgenogram, even in the case of a radiotransparent foreign body because of the local changes produced by its presence. The roentgenogram must be made with care because if too light, for example, a metallic foreign body may occasionally escape detection. In case of any reasonable doubt concerning the diagnosis, bronchoscopy is mandatory. Since the advent of the sulfonamide compounds and penicillin, the danger of bronchoscopy in competent hands has been greatly reduced. I completely disagree with the statement of Vinson [20] that penicillin or sulfadiazine should not be administered to patients who have aspirated a foreign body as a prophylactic measure before bronchoscopy. I do this routinely and have never experienced any difficulty which could be attributed to this procedure. To infants and very young children administration of penicillin or sulfadiazine, or both, may be started eight hours before bronchoscopy and continued for twenty-four hours afterward or as long as may be indicated by the child's condition.

As far as asthmatic bronchitis is concerned, I regard this condition in infants and children as essentially a forerunner of bronchial asthma. In every case I have observed in which recurrent attacks of asthmatic bronchitis have persisted, bronchial asthma has eventually developed in the child. For this reason I feel that recurrent asthmatic bronchitis should be studied in exactly the same manner as one studies bronchial asthma.

Among other conditions which enter into the differential diagnosis of bronchial asthma in infancy and childhood are [17]: cystic fibrosis of the pancreas; thymic "asthma"; Ayerza's disease; dust bronchitis; sighing dyspnea; bronchostenosis, and bronchotetany. Fortunately, cardiac asthma rarely occurs in childhood and, therefore, is almost never a problem in differential diagnosis. The youngest patient White [21] ever saw with cardiac asthma was 18 years of age. At the Strong Memorial Hospital, in Rochester, N. Y., 2 patients were observed by Clausen,[22] one 12 years of age and one 11 years of age.

Laryngologic Consultation.—Consultation with a laryngologist should be a routine procedure in the study of a child with respiratory allergy. This should include examination of the nose, sinuses, adenoids, tonsils and pharynx. The work of Crowe,[23] recently reviewed

20. Vinson, P. V.: What the Physician Should Know About Foreign Bodies That Have Been Swallowed, Am. Pract. **1**:211, 1946.

21. White, P. D.: Personal communication to the author.

22. Clausen, S. W., cited by Glaser.[17]

23. (*a*) Crowe, S. J.: The Nasopharynx, Arch. Otolaryng. **33**:618 (April) 1941; (*b*) The Local Use of Sulfadiazine Solution, Radon, Tyrothricin and Penicillin in Otolaryngology, Ann. Otol., Rhin. & Laryng. **53**:227, 1944.

by Gay,[24] indicated that nasopharyngoscopic study is of great importance. Even after adequate removal of the tonsils and adenoids, if infections continue to recur, the posterior and lateral walls of the pharynx may become studded with nodules of lymphoid tissue, a condition commonly described as "granular pharyngitis." Infections of these follicles may act as a trigger mechanism for touching off attacks of asthma. Nasopharyngoscopy will often show the same condition more frequently and in a more advanced stage in the nasopharynx. Because in this region lymphoid tissue is an integral part of the mucous membrane, it cannot possibly be removed completely unless the entire thickness of mucous membrane is taken out, which, of course, is impossible. The recurrence, therefore, of adenoid tissue in the nasopharynx is not due to previous faulty surgical treatment but is the normal physiologic reaction. The treatment for recurrence is not a second operation but irradiation. For this purpose Crowe [23b] advised radon. This is especially valuable in treating recurrences of lymphadenoid tissue which may block the internal ostiums of the eustachian tubes and thus cause impairment in hearing.

Next to the sex cells, the lymphocytes are the most sensitive cells in the body to beta and gamma irradiation. Therefore, in treating these patients, the dosage employed is so small that there is no danger of a burn or a dry nasopharynx. Under irradiation treatment the lymphoid mass gradually shrinks and finally disappears, leaving a smooth mucous membrane not unlike that of the nasal septum. This method of treatment, Crowe pointed out, is of the utmost value in treating children who have recurrent infections of the upper respiratory tract which are apparently due to recurrent or persistent infection of the follicles of lymphadenoid tissue in the pharynx that have not been removed surgically and are not amenable to surgical treatment.

However, it is only fair to say that the treatment of such conditions with radium or radon must be carried out by a specialist who is thoroughly skilled in this technic and that careful attention must be paid to the amount of exposure to radiation or a burn resulting in a dry pharynx may occur. The use of this technic in children 3 or 4 years of age or less is often difficult and sometimes impossible. The evidence suggests that equally good results may be obtained by the proper use of the roentgen ray. Swihart [25] reported on a small series of such cases. Roentgen therapy was also particularly advocated

24. Gay, L. N.: The Treatment of Residual Lymphoid Tissue in the Nasopharynx by Radium, J. Allergy **17**:348, 1946.

25. Swihart, L. F.: Upper Respiratory Infections in Children, with Special Reference to Involvement of Lymphoid Tissue, J. Indiana M. A. **38**:488, 1945.

by Rosenblum, Pearlman and Uhlmann.[26] The results are exceedingly good as regards the reduction of lymphoid tissue, and there appears to be no danger in competent hands. It would appear that if the two technics produce equally good results, then certainly the pediatrician will prefer to have his patients treated by a roentgenologist rather than suffer the discomfort and perhaps run the greater risk of treatment by the laryngologist. Included in the physical examination should be a fluoroscopic study of the chest and routine tuberculin and Schick tests.

After the history has been taken and the physical examination completed, there are always certain questions which the parent wishes to ask the physician. One of the commonest of these is, "Doctor, will my child outgrow this even if we do nothing about it?" The answer to that question is that, although many children will outgrow their allergy, there is no way of foretelling which children will or will not do so. It is a tragic experience for a girl with eczema, for example, to pass through puberty into young womanhood with a diseased skin. The psychic trauma in such cases is often far out of proportion to the allergic disease. Every effort should be made to clear the child's skin as soon as possible and to continue to keep it clear.

In the case of asthma the disability resulting from the persistence of the disease may be so severe that there should be no question regarding a persistent search for relief. The dictum of the Duchess,[27] slightly modified, should never be followed:

> Speak roughly to your little boy,
> And beat him when he wheezes;
> He only does it to annoy,
> Because he knows it teases.

It should further be explained to the parents that no matter what the presenting complaint is, it is only one phase of a cycle which may go on, with varying manifestations and with varying degrees of intensity, for the rest of the patient's life. The object of the study is not only to relieve the present complaint but to outline a way of life which has a reasonable chance of relieving the present condition and perhaps preventing the development of other and perhaps worse allergic diseases and their complications.

Another question almost always asked by the parent of a child who has severe asthma is, "Doctor, will this affect my child's heart?"

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26. Rosenblum, P.; Pearlman, S. J., and Uhlmann, E. M.: Seminar Discussion of Irradiation Therapy of Tonsils and Adenoids, Hosp. Management **60**:120, 1945.

27. Mirvish, I.: Differential Diagnosis and Treatment of Asthma in Childhood, South African M. J. **16**:431, 1942.

For many years allergists have felt that asthma, even when it occurred severely and for long periods of time, did not adversely affect the heart of the child. It remained, however, for Derbes and Englehardt [28] only recently to prove this impression by acceptable scientific studies.

The question is often asked, "Is my child's asthma likely to make his lungs more susceptible to tuberculosis?" Here again the answer, based on clinical experience, is that as far as children are concerned, asthma does not predispose to tuberculosis. This, however, has not been subjected to analytic study as in the case of adults; the report of Tocker and Davidson [29] showed that the incidence of tuberculosis in asthmatic adults is no greater than the incidence of tuberculosis in the general population.

If the child has had asthma for a long time, particularly if he is in an almost continuous state of status asthmaticus, the parent often asks whether it would not be better to try to build up the child physically before subjecting him to cutaneous testing and other diagnostic and therapeutic procedures. This, however, is putting the cart in front of the horse. The child must first be relieved of his asthma. If this can be done, his restoration to a good state of nutrition may be assured.

DIAGNOSTIC PROCEDURES

In infants, even up to 1 year of age, it is not particularly essential to begin cutaneous testing immediately. In the case of out of town patients for whom repeated visits would work a hardship, it is well to begin them so that a complete report may be submitted to the referring physician. However, if one can see these patients at fairly frequent intervals without too much discomfort to them, it is not necessary to proceed immediately to cutaneous testing. Directions should be given for environmental control, local therapy prescribed and a trial diet started. Directions for environmental control should specifically enable the patient to minimize exposure to house dust, feathers, wool, silk and pyrethrum. Other special directions may be given as a result of leads obtained in history taking and subsequent progress notes, and as a result of the cutaneous tests when these are done.

The principle of the trial diet is to eliminate foods which most commonly cause trouble and to administer to the child those foods which

28. Derbes, V. J., and Englehardt, H. T.: Roentgen Studies of the Heart in Asthmatic Children, J. Pediat. **25**:394, 1944. Englehardt, H. T., and Derbes, V. J.: Electrocardiographic Studies in Asthmatic Children, ibid. **26**:160, 1945.

29. Tocker, A. M., and Davidson, A. G.: The Relationship of Bronchial Asthma (and Hay Fever) to Pulmonary Tuberculosis, J. Allergy **15**:108, 1944.

rarely cause trouble. A simple elimination diet for a child 1 year of age or less may be devised as follows:

1. Cow's milk substitute
2. One single cereal, as oatmeal
3. Two vegetables—carrots and string beans
4. Two fruits—apple and pear
5. One meat—capon or rooster
6. Vitamin preparations, such as provatol® and cecon®

If the child has to have crackers, then Ry-krisp® wafers may be used and the ground wafers may also be used as a cereal. Provatol,® which consists of provitamin A (carotene) and irradiated ergosterol from plant sources dissolved in sesame oil, is an adequate substitute for cod liver oil, and cecon,® which consists of a 10 per cent solution of ascorbic acid in propylene glycol, may be used to supply vitamin C instead of orange juice, or, crystalline ascorbic acid may be used. Naturally, nothing should be used in the trial diet which is contraindicated by the history or the results of the cutaneous tests.

Cutaneous Testing.—Since the parent often has the idea that cutaneous testing is a scientific procedure of great accuracy by means of which it is possible to determine exactly what causes the child's trouble, it is important to explain in advance that such is not the case. It should be explained that cutaneous testing is merely a laboratory procedure, which, in spite of the drama attached to it, is of considerably less value than a carefully taken history. Testing is necessary because it often gives aids which are time saving and of great help in the conduct of the case. Like the physical examination, fluoroscopy and other tests, it is just another aid in the diagnostic study.

The question is often asked, "What is the lowest age limit for skin testing?" While it is often possible to conduct a case properly without cutaneous testing until the child is 1 year or more of age, there is no objection to testing at any age. In the case of breast-fed infants even 6 or 8 weeks of age, and often younger, the skin will often react to foods in the mother's diet, and the condition of the infant will generally be improved when positively reacting foods are omitted from her diet. In the case of bottle-fed infants the skin will often be observed to react to foods which the child has not yet ingested. This gives important information as to what foods not to feed as the child develops, as will be mentioned subsequently.

The technic of cutaneous testing in infancy and childhood is not particularly difficult. The main problem, of course, is to have the child held as still as possible. The next most important prerequisite is that the tests be done by one skilled in the technic. For cutaneous testing in children up to the age at which they will commonly hold

still enough for accurate testing to be done without restraint, usually at about 5 or 6 years, I use a specially devised table. This is a small examining table which has an extensible head rest. All the clothes except the diaper or shorts are removed from the child, who is tightly wrapped in a cotton sheet from just above the hips down to the ankles. A canvas belt 5 feet long (152.4 cm.) and 14 inches (35.6 cm.) wide is now passed over the child's legs. There are three straps for fastening down this belt. The middle strap is lined up to pass over the child's knees and this must be pulled rather tightly. The other straps may be pulled less tightly, but the lower strap must be pulled tightly enough that the child cannot work his feet up underneath the belt.

The mother sits at the head of the table and her task is particularly important. She must hold the child by the elbows which should be held tightly against the child's ears. The child cannot be held properly by the wrists, as practically every mother will attempt to do and will often persist in attempting despite repeated efforts at explanation. A child held in the proper position will still be able to move more or less, but the movements are greatly restricted and tests can be done accurately if the technician is skilful enough.

It is my practice in any age group to do scratch tests first. The advantages of this are so apparent that it is difficult to understand why many allergists do only intradermal testing, even in children. The first and most important reason for doing scratch tests is that these are much safer than intradermal tests. There are 2 deaths from scratch tests mentioned in the literature,[30] but I have never been able to authenticate them. On the other hand, at least a dozen deaths resulting from intradermal testing are mentioned in the literature, and many more deaths have occurred which have never been reported.

The second reason for doing scratch tests first is that they may eliminate the necessity for doing many intradermal tests. If the reaction to the scratch test is positive, then of course it is evident that an intradermal test with that particular substance is not necessary. On the other hand, if the reaction to a properly done scratch test is negative, an intradermal test may be safely performed with the strongest available material which will not give a nonspecific, irritative false positive reaction. This will eliminate testing with serial dilutions of potent allergens, such as cottonseed, for example.

With scratch tests as with intradermal tests, false positive reactions are much more likely to occur than false negative reactions so that

30. Vaughan, W.: Practice of Allergy, ed. 1, St. Louis, C. V. Mosby Company, 1939, p. 171.

it is exceedingly important to check positive reactions, whether from scratch or intradermal tests, repeatedly to make sure that the reaction is actually positive and is not a false positive.

A third reason for doing scratch tests first is the greater irritability of the skin of children. If one does only intradermal tests, many false positive reactions will be reported. This is particularly important in children, although the same thing often happens with adults. Not infrequently children are studied who have previously passed through the hands of an allergist who makes only intradermal tests. When one asks the mother what tests were reported as giving positive reactions, she states that the physician said that everything elicited them. Of course, reporting that everything causes positive reactions is practically the same as saying that everything causes negative reactions, for all the value such tests have. However, not infrequently these children may be satisfactorily tested by means of the scratch method.

The instrument preferred for making the scratches is the leather punch adapted for this purpose by Hill.[31] This is a metallic instrument about the size and shape of a small pencil, with the lead replaced by a circular opening a little more than 2 mm. in diameter. The edges are fairly sharp so that with one quick rotary motion a small circular scratch is made in the skin. The advantages of this instrument are several. In the first place, it does not look like a knife or cutting instrument so that a child is not frightened by its appearance. Second, the scratches are always the same size and shape. Third, it is difficult to traumatize the infant with this instrument unduly so that, if the child makes a quick movement while the scratch is being made, little damage can be done. With experience it is possible to make these scratches rapidly and accurately, even in a small infant who is struggling more or less in spite of the restraint. Hill[32] himself no longer uses this device, preferring instead a three cornered needle. This emphasizes the fact that it is of little importance what type of scratching device one employs as long as one is expert in its use.

A buffered isotonic sodium chloride solution[33] is used for dissolving the powdered allergens applied to the scratches. The procedure is, first, to drop this liquid on the scratch. Then the powder is applied. By putting the liquid on before the powder, there is less danger of shaking the powder away from the scratch by the struggling of the child. Unbuffered isotonic sodium chloride solution may be used as well as the buffered solution. I do not use tenth-normal sodium hydroxide solution recommended by many because I feel that this often acts as a

31. Hill, L. W.: Infantile Eczema, J. Pediat. **2**:133, 1933.

32. Hill, L. W.: Personal communication to the author.

33. Evans, A.: A Buffered Physiologic Salt Solution, J. Infect. Dis. **30**:95, 1922.

nonspecific irritant. At one time I tried using glycerinated extracts so that evaporation would be minimized, making it unnecessary to watch the test powders carefully to keep them from drying out, and because the viscosity of the mixture made the test material stay in place better than the aqueous solution. However, I had the impression that many false positive reactions were given by the glycerin, so now I no longer use it except in testing with Efron [33a] house dust extract and when this is done a control test is always made.

The indications for passive transfer tests are the same in any age group. My only variation from the orthodox procedure is that I always try to use two recipients, as it is often amazing to observe how differently they may react under the same conditions. No objection has been found to using the parents or other blood relatives of the child.

The question arises as to how many tests one should do. There is no truly sound objection to the practice of many of making tests with everything conceivable for which test material may be prepared because, on rare occasions, a positive reaction will be elicited by some allergen which appears to have no connection at all with the case. On closer investigation it may be found that this is one of the substances which is really causing trouble. However, this happens so rarely, and the diet and environment of the infant and child are so small as compared with those of the adult patient that I feel it is an injustice to subject these children to so-called complete testing. One should test for those substances indicated by the history as possible causative factors, as well as for those substances indicated by experience as often causing trouble in this age group. These substances would include all the foods which the child ingests and also those foods which it is planned to feed him next. It will occasionally be observed, as has been mentioned, that a child will react to some food which he has not yet had. In such circumstances it does not make much sense to try this food in the child's diet, even though he may not be clinically sensitive to the food at the time it is tried. I believe that this is just an invitation to trouble. The child should also be tested with house dust, wool, silk, feathers, cottonseed, kapok, flaxseed and those other allergens which are particularly indicated, as mentioned previously, by the history of the case. In this age group flaring occurs oftener than whealing but is of equal diagnostic significance. There is no such thing as a standard-sized flare or wheal which is 1 plus when it measures so much and 2 plus when it measures so much more and so on. Every child has his own standard of reaction, and one must discover what this is by comparison with reactions which are the least prominent and have no clinical significance.

33a. Boatner, C. H., and Efron, B. G.: Studies with Antigens; Preparation and Properties of Concentrates of House Dust Allergen, J. Invest. Dermat. 5:7, 1942.

Diphenhydramine (benadryl®) and hydrochloride tripelennamine (pyribenzamine®) hydrochloride may be used to reduce the hyperirritability of the skin, but, generally speaking, this is not particularly satisfactory. Incidentally, infants and children tolerate these drugs fully as well as adults.

PROGRESS NOTES

One of the most valuable aids in the study of any case is the keeping of careful notes on the patient's progress while under observation for cutaneous testing. The parent should be carefully queried as to how the child has done in the intervals between his visits to the office. One of the most important things which the allergic study accomplishes, particularly a carefully taken history and follow-up notes, is to educate the parent to look at the child through the eyes of the allergist. She subconsciously looks for the answers to the questions which were previously asked in the formal history taking and in the follow-up notes: What foods do you know actually bother the child? What contacts? What drugs? What meteorologic factors? This constant search for relevant factors should be encouraged. Carefully taken progress notes will reveal many new facts, besides the effect of whatever therapeutic measures may be attempted.

FINAL REPORT

Now, having examined and tested the child completely, what is the next step? I believe it is then time for the allergist to sit down and evaluate the patient's record carefully. The first thing to do is to put down the final diagnoses, as well as these can be established. They should be noted on the first sheet of the record so that the cases may be carefully indexed and cross indexed.

The next procedure should be to write out specific directions for the patient. I do not believe that an allergist who simply examines and makes tests on a patient and then gives him a list of the reactions and a brief discussion of their significance is doing his full duty. I am a firm believer in giving the patient highly detailed directions as to the conduct of his own particular case. The objection to the former procedure is that the parent will forget what she has been told; the objection to the procedure here advocated is that the parent often will not read the directions which have been given.

A lesson was learned regarding this and how to combat it in an interesting manner. At the completion of a study of a child with chronic atopic dermatitis the parents had been given detailed typewritten directions as to the conduct of the child's case at home. In the course of many months the fee for this study was not paid. The reason for this, the mother

stated, was that, after leaving my office, the child had not improved and so had been taken to a dermatologist who had advised that all wool be removed from the child's immediate environment. The parents did this and, greatly to their gratification, the child's skin rapidly cleared. On a check of the child's history, which contained a complete carbon copy of all instructions given the parents, it was found that the first paragraph gave specific directions for the avoidance of wool. It was obvious that the parents had not read the detailed instructions which they had been given.

From that time on the office procedure was somewhat different. I still wrote out specific directions for the patient, supplying the parent with forms as far as possible for the avoidance of specific allergens, such as house dust, cottonseed, flaxseed, orris, and the various epidermoids, but when the patient was presented with this information, she was first told that the instructions given always looked like considerably more work and trouble than they actually were in practice. If the directions were carefully followed, she would soon learn which particular instructions were relatively of the most importance to her own child, and the habit of following these would soon become easy. She was further told that even though the directions were extremely difficult to follow, which they occasionally are, it would be well worth the effort, as this may be the only means for relieving the child of his difficulty.

The parent was then asked to sit down in the waiting room and read the directions over carefully and was then again received into the consulting room and asked if there were any questions. If the parent had no questions, then I began quizzing her to see how much she understood of the directions. In the case of a particularly dull parent or in cases in which there was a great deal of this to be done, a capable secretary was often able to take over much of the burden.

In many instances the referring pediatrician or general practitioner expects the patient to be sent back to him with treatment material and specific directions for administration, if injections are required for the proper conduct of the case. When the patient comes from out of town and facilities are not available for treatment by an allergist, this is proper as well as necessary. When, however, it is just as convenient for the patient to be treated by the allergist who has made the study, it is often a grave injustice to the patient to be compelled to return to the referring physician for treatment. There is considerably more to the treatment of allergic disease than the blind following of a printed instruction sheet, however explicit the directions may be.

It is my firm belief that one cannot be too explicit in giving complete directions. One never knows just how a patient may be exposed to

any one particular allergen. For example, in the directions for avoiding rabbit fur, I mention that some persons occasionally carry a rabbit's foot in their pocket for good luck. One woman whose child had asthma and allergic rhinitis and gave a strong reaction to rabbit dander called up the office in great excitement to state that she had discovered at least one factor in her infant's difficulty. When the child was a few months old, a well meaning relative had given him a rabbit's foot which had become a fetish. The child would not go to sleep without rubbing it back and forth over his upper lip. While removing the rabbit's foot from this child's environment did not answer all the questions in this particular case, at least it went far in solving many of them.

The introduction of penicillin aerosol in the treatment of bronchial asthma may prove to be one of the most important therapeutic contributions which has yet been made to the study of the condition. Every child, or adult for that matter, who does not respond to the usual allergic study and who appears to have asthma associated with infection should have a trial with penicillin aerosol. This procedure is being exhaustively investigated throughout the country. I have observed a few children who did not respond to the most thorough study and treatment from the standpoint of allergy. They have, however, responded excellently to the use of penicillin aerosol. My present method of treatment does not differ greatly from that which has been described by others, except that perhaps the doses used are larger. I start with 100,000 units administered daily or several times a day during one week in the office or at home. As a general rule, if a patient is going to show improvement, this will occur within that length of time, although sometimes it may take a little longer. If the patient does show unmistakable improvement, the parent is then taught the administration of the penicillin aerosol at home by the use of the hand, bulb or bicycle pump,[34] or by positive oxygen or air pressure, and instructed to continue this until the child has been free from asthma for a reasonable length of time, as three or four weeks. The dosage is then gradually reduced and the intervals between treatments increased. By this means I believe that I have helped many asthmatic persons. Whether or not the results will be permanent and whether or not trouble will develop from penicillin-fast organisms, only time will tell.

A new epinephrine-like preparation, butanefrine® (racemic 1[3,4-dihydroxyphenyl]-2-amino-1 butanol hydrochloride), appears to have some distinct advantages over epinephrine. It has no pressor effect, and side reactions such as tremor and tachycardia are greatly minimized, at

34. Finke, W.: Simplification of Penicillin Aerosol Therapy for Home Treatment, Am. Pract. **1**:643, 1947.

least in children. This drug is not, however, as effective as epinephrine in controlling really severe attacks of asthma.

PROPHYLAXIS OF ALLERGIC DISEASE

As was stated earlier in this discussion, the contribution which the pediatrician should specifically seek to make to the knowledge of allergy is to learn as much as possible concerning what may be done for the prophylaxis of allergic disease. This is in line with the general contributions that pediatrics has made to medicine in the past few decades which have been of such tremendous importance to the human race. Every allergist will acknowledge that with but few exceptions, if the history is taken carefully enough, the beginnings of allergic disease in the adult may be traced back to early childhood or even infancy. It is perhaps some exaggeration to say, as I did some years ago [35] in attempting to obtain certification for pediatricians in allergy as well as for internists, that if pediatricians do their job well enough the occurrence of allergic manifestations in adult life will eventually be looked on as the result of poor pediatric care in infancy and childhood. Time does not permit complete discussion of what is known or thought to be known about the prophylaxis of allergic disease. It is fair to state only that this knowledge is thus far purely empiric and whether it has practical value will take many years to determine. However, these measures can do no harm and, because it is possible that they may be productive of great good, they are well worth trying.

The attempt at prophylaxis should begin as early as possible in pregnancy. I ask pregnant mothers in families with known allergy to follow these directions:

1. Every effort should be made to breast feed the baby as completely as possible. The completely breast-fed infant has seven times as many chances of escaping eczema as the bottle-fed baby.[36]

2. The mother should eat no eggs during her pregnancy. This does not mean she should be on an egg-free diet, but eggs as such and foods consisting largely of eggs, as angel cake or custard, should be avoided.

3. She should not drink an excessive amount of cow's milk. A pint a day should be given, preferably boiled ten minutes. In addition to this, calcium and phosphorus should be supplied in adequate amounts from other sources.[37]

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35. Glaser, J., in discussion on Recommendations of the Advisory Board of American Allergists on Training for Certification in Allergy, J. Allergy **14**:91 1942.

36. Grulee, C. G., and Sanford, H. N.: The Influence of Breast and Artificial Feeding on Infantile Eczema, J. Pediat. **9**:223, 1936.

37. Two or three capsules containing 725 mg. dicalcium phosphate, 30 mg. ferrous sulfate, 2 mg. thiamine hydrochloride, 2 mg. riboflavin and 400 U. S. P. units vitamin D are given three times a day.

4. The mother who is herself allergic should avoid those foods and other allergens which she knows cause her trouble.

5. She should eat a wide variety of food and not concentrate, as pregnant women occasionally do, on just a few articles of diet.

6. The mother should continue to follow these instructions as long as the infant is breast fed.

The pediatric allergist should be placed in charge of the potentially allergic infant as soon as he is born, and nothing should be fed the infant except by the allergist's order. If the mother cannot nurse, I prefer to start feeding the infant on soybean milk rather than cow's milk.[38] The reason for doing this is that the infant tends to become sensitized to whatever food enters the gastrointestinal tract first, owing probably to physiologic immaturity of the tract and its accessory organs. Why feed a potentially allergic newborn infant such a common and important food as cow's milk and allow him to become sensitized to that when a less common food will nourish the child just as well? If sensitization is acquired to that food, it is not too important and the infant can be gradually changed over to a cow's milk formula after the gatsrointestinal tract has attained a certain degree of maturity. It is sometimes much more difficult to start a newborn baby on soybean milk than on cow's milk but, as has been emphasized, the pediatric allergist must also be an exceedingly well trained pediatrician.

When vitamins are to be added to the child's diet, I prescribe provatol.* This supplies vitamins A and D. Allergic reactions in infants from cod liver oil were described by Balyeat and Bowen [39] and by Hoffman and Rattner,[40] so until such reactions have occurred with the use of this preparation, I shall continue to prescribe it.

I do not give these children orange juice, as sensitivity to this is easily acquired, although fortunately it rarely appears to cause allergic manifestations severer than slight transient urticaria or a minimal atopic dermatitis. Instead I use either crystalline ascorbic acid or cecon.*

When the time comes to start cereal, I do not give mixtures such as pablum,* which contain a great variety of potential allergens. Pablum,* for example, contains the following: wheatmeal (farina), oatmeal, wheat germ, cornmeal, powdered beef bone, alfalfa leaf and dried brewers' yeast. Why take the chance of sensitizing the child to so important a food as wheat in such a mixture? Instead I prescribe a single pure cereal, particularly oatmeal or barley. This will serve the purpose of

38. A series of infants so treated will form the subject of a subsequent communication.

39. Balyeat, R. M., and Bowen, R.: Cod Liver Oil Sensitivity in Children, Am. J. Dis. Child. **47**:529 (March) 1934.

40. Hoffman, S. J., and Rattner, H.: Infantile Eczema from Cod Liver Oil: Report of Two Cases, J. A. M. A. **107**:494 (Aug. 15) 1936.

feeding cereal just as well while the gastrointestinal tract is maturing, and if the child does become sensitized to either of these cereals, it will not cause nearly as much trouble as though he were sensitized to wheat.

When vegetables are started, most pediatricians begin with vegetable soup, which is a mixture of a number of vegetables. I prefer to start with one vegetable, gradually adding others until the child gets a reasonable variety, and then a mixture of these vegetables in the form of a soup may be tried. Fruits are added later, one at a time.

Egg should not be added until the child is at least 9 months of age, and if the child has had eczema or other allergic disease, I do not add egg until much later, at about 1 or 1½ years of age. When egg is added, the child should be given one quarter of a hard-boiled egg yolk three times a week. If this agrees, one-quarter more of the yolk is added weekly until the child gets a hard-boiled yolk three times a week. Then a small amount of hard-boiled eggwhite is added and the proportion gradually increased until the child gets a whole hard-boiled egg three times a week. If this agrees, egg in other forms may be tried and usually successfully. Fish is started between 9 months and 1 year of age and the child changed to pasteurized milk at the age of about 1 year.

There is no reason at all for giving the child chocolate until he is 2½ or 3 years of age and at that age friends and neighbors will insist on giving the child chocolate candy anyway. The same holds true for nuts of various kinds.

The prophylaxis of diphtheria, tetanus and pertussis is of paramount importance to every child but especially important to the allergic or potentially allergic child. It should be emphasized to those dealing with children that the presence of an allergic disease does not contraindicate any of the routine prophylactic measures except smallpox vaccination in the case of the eczematoid dermatoses. It is important that the allergic child be immunized against diphtheria and tetanus so that he will never need the corresponding antitoxin. If tetanus toxoid has been omitted in the case of an allergic child and tetanus antitoxin is indicated, the bovine preparation [41] should be used if available, unless the child is allergic to milk or beef. Unfortunately, the manufacture of bovine antitoxin has been discontinued in this country but occasionally some may be obtained. Since it is lyophilized, it keeps indefinitely, even without refrigeration. If the bovine antitoxin is not available, despeciated horse serum tetanus antitoxin should be used. Despite the so-called despeciation, this preparation must be administered with extreme care.

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41. Glaser, J.: The Use of Bovine Antitoxin for the Prophylaxis of Tetanus, J. Pediat. **19**:403, 1941.

Hypoimmunization against pertussis is important because the allergic child is likely to acquire respiratory allergies. If such a child contracts whooping cough, the disease may aggravate a clinical or subclinical respiratory allergy. Asthma particularly may be initiated or aggravated. It is important that a phase I pertussis vaccine be used and that it be grown on media prepared with human rather than animal blood to avoid sensitization to a foreign protein. Booster doses of pertussis vaccine should be given yearly until the child is at least 5 years of age. If whooping cough does develop, it should be vigorously combated with antipertussis serum (human), obtainable commercially (hypertussis®), or by the use of pertussis immune serum (human) N. N. R., which may be obtained from the Philadelphia Serum Exchange.[42]

A child with atopic dermatitis should not be vaccinated until the skin is perfectly clear. The reason is that for a few days after vaccination the virus is carried about in the blood stream and tends to localize in any areas of diseased skin. This may produce a generalized vaccinia which may be serious and occasionally disfiguring or even fatal. How long after the skin is clear it is safe to perform smallpox vaccination is a debatable point. In my own practice I commonly vaccinate two or three weeks after the skin is perfectly clear and have never had any trouble from this source. It is also important that no fresh vaccinations be made on children in homes where other unvaccinated children have atopic dermatitis. Contact of the skin of these children with a fresh vaccination wound may inoculate the atopic child, resulting in a generalized vaccinia. The contact may also be indirect, as from a soiled towel or wash cloth. One death occurred from generalized vaccinia in a hospital of my acquaintance when an infant with atopic dermatitis was bathed in the same tub in which a freshly vaccinated infant had been washed.

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42. Children's Hospital of Philadelphia, 1740 Bainbridge Street, Philadelphia.

PRESENT STATUS OF IMMUNIZATION TO AND TREATMENT OF SCARLET FEVER

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IT IS NOW twenty-three years since the Dicks proved the etiology of scarlet fever and perfected methods by which susceptibility to the disease could be ascertained and by which the disease could be prevented. They also produced a successful antitoxin for treatment of the active phase. It is surprising that immunization to scarlet fever is still a controversial subject. In the present discussion some of the questions still in the minds of physicians about scarlet fever will be examined.

EFFICACY OF IMMUNIZATION TO SCARLET FEVER

Do the present methods of immunization against scarlet fever actually immunize against the disease?

If one specifies the Dick method in which, according to the old formula, unchanged scarlet fever streptococcus toxin U. S. P. was administered in five doses increasing from 500 to 80,000 skin test doses and which, in the past three years, has been increased to an initial dose of 650 skin test doses increasing gradually to a final dose of 120,000, the answer is yes. Reports on immunized and nonimmunized persons in heavily exposed groups—particularly nurses in hospitals for contagious diseases and children in institutions which had outbreaks of scarlet fever—include the data on thousands of subjects. Those persons who have used the dosage indicated in the proper sequence have uniformly reported a solid protection against the disease lasting for several years. For example, I reported, in 1931, on a three and one-half year experience with immunization in which 1,280 undergraduate nurses of the Cook County Hospital, Chicago, were exposed to scarlet fever.[1] Of these nurses 41.6 per cent were demonstrated susceptible and 58.4 per cent immune by the Dick test. Of the susceptible group 298 were immunized by the Dick method. None contracted the disease. One of

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1. Rhoads, P. S.: Skin Tests and Immunization Against Scarlet Fever and Diphtheria, J. A. M. A. 97:153-156 (July 18) 1931.

those reported as having a negative reaction to the original Dick test subsequently contracted scarlet fever. During the same period 15 cases occurred among a group of 449 nurses who either were not tested and not immunized or had only a part of their immunizing series. Since 1931, the figures have not been collected but the immunization has continued. In a nursing population numbering about 1,000, a considerable proportion of which has duty in contagious and children's hospitals, no more cases of scarlet fever have occurred in those with originally negative reactions to Dick tests or in those immunized to the point of a negative Dick reaction, though an occasional case occurs in a nonimmunized nurse. The experiences of Toomey,[2] Hektoen and Johnson,[3] Place,[4] Benson and Rankin,[5] Anderson and Reinhardt,[6] Glazier,[7] Graham,[8] Platou,[9] Rappaport[10] and many others were similar. No one can legitimately question the ability of the Dick method of immunization with scarlet fever streptococcus toxin to immunize against scarlet fever.

EFFICACY OF MODIFICATIONS OF THE DICK METHOD OF IMMUNIZATION

In the past twenty years many modifications of the Dick method have been introduced with the idea of decreasing the number of injections required and lessening the severity of the reactions. These include the ricinoleated antigen of Larson and his associates,[11] Futagi's ana-

2. Toomey, J. A.: Scarlet Fever Immunization, Ann. Int. Med. **15**:959-973 (Dec.) 1941.

3. Hektoen, L., and Johnson, C.: Prevention of Diphtheria and Scarlet Fever in Nurses, J. Prev. Med. **2**:289-292 (July) 1928.

4. Place, E. H.: Result of Active Immunization of Nurses Against Scarlet Fever, Am. J. Pub. Health **28**:137-142 (Feb.) 1938.

5. Benson, W. T., and Rankin, A. L. K.: Active Immunization Against Scarlet Fever, Lancet **2**:1357-1361 (Dec. 15) 1934.

6. Anderson, G. W., and Reinhardt, W. L.: Scarlet Fever Immunization of Nurses, J. Infect. Dis. **57**:136-142 (Sept.-Oct.) 1935.

7. Glazier, M. M.: Active Immunization Against Scarlet Fever, New England J. Med. **233**:204-206 (Aug. 16) 1945.

8. Graham, H. C.: Scarlet Fever Immunization: Evaluation of Some Methods of Scarlet Fever Immunization over a Fifteen Year Period, South. M. J. **35**:132-139 (Feb.) 1942.

9. Platou, E. S.: Scarlet Fever Prevention by Immunization, J. Pediat. **5**: 531-534 (Oct.) 1934.

10. Rappaport, B.: Active Immunization to Scarlet Fever with Less Reaction, J. A. M. A. **106**:1076-1078 (March 28) 1936.

11. Larson, W. P.; Huenekins, E. J., and Colby, W.: Immunization Against Scarlet Fever, with Toxin Detoxified with Sodium Ricinoleate, J. A. M. A. **86**:1000-1001 (April 3) 1926.

toxin,[12] intranasal spray of scarlet fever antigen,[13] inunction of scarlet fever toxin,[14] Veldee's toxin treated with 10 per cent solution of formaldehyde U. S. P.,[15] intracutaneous injection of scarlet fever toxin in relatively small doses,[16] oral administration of scarlatinal toxin [17] and injection of various mixed hemolytic streptococcus filtrates.[3] One by one these procedures have been abandoned because they did not produce solid immunity against scarlet fever or because the reactions were severer than had been anticipated. By 1943 the only preparations available commercially to physicians were packages of scarlet fever streptococcus toxin prepared and marketed according to specifications of the Scarlet Fever Committee in the dosage mentioned previously. However, since release of control of immunizing material by the committee in 1943, modifications of the five dose method of the Dicks have been put on sale—including a preparation of so-called scarlet fever toxoid made by treating scarlet fever toxin with tannic acid.[18] Some of these modified products are divided into three doses instead of five and do not approach the total dosage of scarlet fever toxin formerly specified.

With each of the preparations containing modified or unmodified toxin it was possible to produce a negative Dick reaction in a certain proportion of susceptible persons. But it has been repeatedly demonstrated that immunity against scarlet fever, as against other infections, is a quantitative affair, the degree and duration of immunity depending on the amount of antigen introduced. It was shown earlier that with preparations of so-called scarlet fever toxoid the percentage of susceptible

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12. Futagi, Y.: Improvement of the Prophylactic Immunization Against Scarlet Fever by Means of Anatoxin After Ramon's Method, J. Immunol. **19**:451-456 (Nov.) 1930.

13. Peters, B. A., and Allison, S. F.: Intranasal Immunization Against Scarlet Fever, Lancet **1**:1035 (May 18) 1929. Friedman, E.; Esserman, A., and Black, M. H.: Active Immunization Against Scarlet Fever by Nasal Route, J. Pediat. **5**:504-510 (Oct.) 1934.

14. Martmer, E. E.: Immunization to Scarlet Fever by the Inunction Method: Preliminary Report, J. Pediat. **1**:555-557 (Nov.) 1932.

15. Veldee, M. V.: Purification and Precipitation of the Erythrogenic Factor of Scarlet Fever Streptococcus Toxin and Its Antigenic Value, Pub. Health Rep. **52**:819-829 (June 25) 1937.

16. Kern, R. A.; Crump, J.; Roddy, R. L., and Borow, S.: Scarlet Fever Immunization by Intracutaneous Injection of Scarlatinal Streptococcus Toxin, J. Allergy **9**:125 (Jan.) 1938. Earle, C. A.: Intradermic Immunization Against Scarlet Fever, Illinois M. J. **74**:248-249 (Sept.) 1938. Fisher, S., and Van Gelder, D. W.: Intradermal Immunization: Scarlet Fever, Am. J. Dis. Child. **61**:88-98 (Jan.) 1941.

17. Cooke, J. V.: Enteral Administration of Scarlatinal Filtrate Toxin, Am. J. Dis. Child. **45**:54-57 (Jan.) 1933.

18. Veldee, M. V.: Further Study of the Purification and Tannic Acid Precipitation of Scarlet Fever Toxin, Pub. Health Rep. **53**:909-913 (June 3) 1938.

persons who could be immunized to the point of a negative Dick reaction and the duration of this immunity corresponded to the amount of toxin present before the modifying agent was added.[19] Thus, to date, it has not been satisfactorily demonstrated that a true scarlatinal toxoid exists.

Until a period of several years has elapsed in which the efficacy of the newer modifications of the Dick technic has been tested, it would seem safer to continue immunization with unmodified toxin in five doses, starting with 650 skin test doses and ending with 120,000.

SEVERITY OF REACTIONS

Many persons have questioned the advisability of immunization to scarlet fever because of the severity of reactions to toxin. These reactions include local swelling, redness and pain at the site of inoculation, fever and headache and occasional nausea and vomiting, mild scarlatinal rash of a few hours' duration and pains in the joints in persons who have had arthralgia before. Rarely, there are urticarious lesions from the protein of the culture medium or the end products of the streptococci in the filtrates. Reactions are variable, and it cannot always be predicted which type of reactions will occur and which doses will produce reactions. In 1929 and 1930, I studied a group of 190 nurses, of Cook County Hospital, receiving immunizing injections and observed that the average loss of time due to reactions was 0.239 day per nurse receiving the full course of five injections.[1] Children usually experience more nausea and less joint pains than adults and are incapacitated for a shorter time. Rappaport,[10] Glazier,[7] the Dicks[20] and others pointed out that these reactions may be much diminished or eliminated altogether by giving the immunizing series in seven to ten doses instead of five and making the increases in each succeeding dose less than in the standard procedure. Thus, if a sharp reaction occurs with the first dose, half of the regular second dose may be given next time, then five to seven days later the regular second dose. It is important to emphasize, however, that to produce satisfactory protection an increase in dosage must be given each time and the total dose given must be as much or more than in the standard program.

TYPE OF IMMUNITY PRODUCED

Many persons, while agreeing that one can successfully immunize against the clinical entity recognized as scarlet fever, question the value of the procedure because the subjects are not protected against hemolytic streptococcic infections unaccompanied with a rash. Such objec-

19. Dick, G. F., and Dick, G. H.: Is There a Scarlet Fever Toxoid? J. A. M. A. **103**:1362-1366 (Nov. 3) 1934.

20. Dick, G. F., and Dick, G. H.: Scarlet Fever, Chicago, The Year Book Publishers, Inc., 1938.

tions are comparable to questioning the value of immunization to typhoid because it does not protect against invasion by all types of gram-negative enteric bacilli. They deny the specificity of the many varieties of bacteria within morphologically similar groups.

Gordon [21] and many others took the view that a scarlatinal rash is only one manifestation of invasion of the body by hemolytic streptococci which are not specific. In support of this view are cited milk-borne epidemics of streptococcic infection in which some of the subjects have scarlet fever, others septic sore throat without a rash and, rarely, others have erysipelas.[22] The reason some persons have a generalized scarlatinal rash and others the localized rash of erysipelas, which is certainly a distinct phenomenon, is not explained. Many authors also have cited the fact that scarlet fever in a given epidemic is associated with streptococci of different Griffith agglutinating types as evidence against the specificity of scarlet fever as a disease entity.[22] Further to confuse the picture, others have taken the view that the scarlet fever rash is an allergic response to invasion by hemolytic streptococci, the first infection producing sensitivity to the organism and the second being associated with the rash, and producing immunity to further allergic responses of this type.[23] This view is so far at variance with what is known about allergy and antitoxic immunity that it scarcely merits further comment. If it were correct, a scarlet fever rash would be the single manifestation among the many recognized to be allergic in nature in which an attack conferred a permanent immunity. It would also be the single allergic reaction neutralizable by a specific antitoxin.

Both those persons who question the specificity of scarlatinal streptococci and those who claim the scarlet fever rash is an allergic or anaphylactic phenomenon lose sight of the fact that scarlet fever is a toxic disease in which the distinguishing systemic features are due to the toxin produced at a localized site, usually the throat, by certain strains of hemolytic streptococci. These strains are identified by their ability, when grown in broth to which human blood has been added, to

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21. Gordon, J. E.: Current Epidemiological Aspects of Scarlet Fever, New England J. Med. **221**:1024-1029 (Dec. 28) 1939.

22. Stebbins, E. J.: Scarlet Fever and Related Streptococcal Infections, M. Clin. North America **27**:661-669 (May) 1943. Jorgan, E.: The Epidemiological Significance of Grouping and Typing the Hemolytic Streptococci, Copenhagen, Ejnar Munksgaards Forlag, 1945. Foley, G. E.; Aycock, W. L., and Cox, R. D.: Serologic Types of Hemolytic Streptococci in Scarlet Fever in Massachusetts, New England J. Med. **233**:761-765 (Dec. 20) 1945.

23. Cooke, J. V.: Scarlet Fever: Relation Between Antitoxin in Blood and Skin Sensitivity to Toxin in New-Born Infants and Their Mothers, Am. J. Dis. Child. **34**:969-978 (Dec.) 1927. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: The Dick Test in Military Personnel, with Special Reference to Pathogenesis of Skin Reaction, New England J. Med. **235**:39-43 (July 11) 1946.

produce a soluble toxin neutralizable by specific scarlet fever antitoxin. This toxin cannot be neutralized by antitoxin produced in animals from injections of filtrates of streptococci cultured from lesions of erysipelas, septic sore throat or sources other than scarlet fever.[24] It is only by this property of production of specific toxin that they can be identified and not by Griffith agglutination reactions or Lancefield typing. Persons who have a small area of scarlet fever rash at the site of intradermal injection of dilute scarlatinal toxin (a positive reaction to the Dick test) in nearly every instance show a typical scarlatinal generalized rash when infected by scarlatinal streptococci, after which the cutaneous reaction becomes negative, indicating an antitoxic immunity to this disease.

If the ability to produce a scarlet fever rash were the only property of scarlet fever toxin, the value of immunization against it could be questioned. However, the invasiveness of scarlet fever streptococci depends in part, at least, on the toxin, as evidenced by the numerous reports of the reduction in complications and mortality in patients with scarlet fever when the antitoxin was used promptly.[25] If immunization to scarlet fever accomplished only protection against erythrogenic toxin, one would also expect, in nurses at contagious disease hospitals and in persons in other situations where close contact with scarlet fever is inescapable, that in immunized subjects the normal quota of ordinary hemolytic streptococcic sore throats would be augmented by the same number of "scarlatina sine exanthem" cases as were usually recognized as scarlet fever prior to immunization. Such has not proved to be the case. In fact, the incidence of even ordinary nonspecific hemolytic streptococcic sore throat has been materially reduced in immunized groups, as shown by the reports of Toomey,[2] Hektoen and Johnson,[3] Place [4] and Benson and Rankin.[5] My own experience has been similar.

If immunization against scarlet fever protected against the erythrogenic action of scarlet fever toxin alone, one would also expect that in persons suffering from invasion by scarlatinal organisms without an accompanying rash the complications would be as serious as in patients with scarlet fever. Afremow and I, in a clinical and statistical study of sore throats in nurses of the Cook County Hospital,[26] compared the complications of ordinary nonspecific hemolytic streptococcic sore throat with those of scarlet fever in a similar age group over the same

24. Hektoen, L.: The Specificness of Certain Hemolytic Streptococci, J. A. M. A. **105**:1-2 (July 6) 1935. Dick and Dick.[20]

25. Hunt, L. W.: Treatment of Scarlet Fever with Antitoxin, J. A. M. A. **101**: 1444-1447 (Nov. 4) 1933. Dick and Dick.[20]

26. Rhoads, P. S., and Afremow, M. L.: Clinical and Statistical Study of Sore Throat in Young Adults, Arch. Path. **26**:403-410 (July) 1938.

period. Although the percentage of total complications was about the same in the two groups (53.4 per cent in the group with sore throat and 55 per cent in the group with scarlet fever), the severity of the complications was quite different. In the group with scarlet fever otitis media was twice as frequent and nephritis five times as frequent as in the group with nonspecific sore throat. Two patients with scarlet fever died, while there were no deaths in the other group.

The Dicks showed that mice immunized with scarlet fever toxin alone were protected from doses of scarlatinal streptococci which, when injected into controls, constantly produced fatal infection.[20]

The exact number of distinct clinical syndromes which hemolytic streptococci may produce cannot be determined in the present state of knowledge. However, scarlet fever and erysipelas are two clinically distinguishable conditions known to be caused by members of the group. The toxins produced by organisms isolated from these two diseases have been shown to be distinct because the antitoxin produced by each neutralizes its own toxin but not the toxin of the other. Until it can be shown experimentally that Streptococcus from a lesion of erysipelas can produce scarlet fever and Streptococcus from a patient with scarlet fever can produce erysipelas, it seems logical to accept these diseases as distinct etiologically as well as symptomatically. The assumption that all hemolytic streptococcic infections are potentially scarlet fever (whether a rash is present or not) and should be prevented if antitoxic immunity to scarlet fever is effected is unwarranted on the basis of facts now available.

TREATMENT OF SCARLET FEVER

For the treatment of the attack the physician has at his disposal sulfonamide compounds, penicillin, convalescent serum and specific antitoxin. A full discussion of the many reports on the use of these agents is impossible in this communication. In summary, it may be said that sulfonamide drugs do not alter the toxic phase of the disease and complications frequently develop while they are being administered in full doses. Paradoxically, however, complications which develop in this manner, of which otitis media and cervical adenitis are the best examples, clear up promptly without suppuration if the sulfonamide compound is continued. Many authors, therefore, take the position that sulfonamide drugs should be withheld until complications begin, then administered in full doses. One cannot argue logically against this view, nor can one object to giving sulfonamide drugs (with the usual precautions) from the start. Chemotherapy has not been demonstrated to reduce the duration of the carrier state.

Most authors agree that penicillin has more effect on the early phases of scarlet fever than sulfonamide compounds and that in full

doses it cuts down the complications in some degree. I observed in a follow-up study of cases of scarlet fever that use of penicillin was more effective than any other treatment in terminating the hemolytic streptococcus carrier state.[26a] For permanent termination of the carrier state, Epidemiology Unit Number 82 of the United States Naval Hospital, Treasure Island, Calif.,[27] reported that a total dose of about 500,000 units was required. Spink, Rantz, Boisvert and Coggeshall[28] concluded that 500,000 to 1,000,000 units was required for this purpose. The latter group considered scarlet fever antitoxin more effective in treating the disease than penicillin.

Scarlet fever convalescent serum, if given early and in adequate amounts, is effective therapy. It may contain antibodies other than antitoxin in greater concentration than the serum from hyperimmune horses and, of course, has the advantage of being a homologous serum. It is harder to obtain than commercial antitoxin and often is given in inadequate dosage. For best results, a minimum of 60 cc. to very young children, up to 200 to 300 cc. for young adults who are quite ill, should be used. Gasul and I showed that the average pooled preparations of convalescent serum contained about 500 antitoxic units per cubic centimeter as compared with 150,000 to 200,000 neutralizing units per cubic centimeter in commercial antitoxin.[29] Many reports of large series of cases with controls attest to the value of both convalescent serum and antitoxin in reducing the incidence of complications, the efficacy being directly proportional to the promptness with which the serum is given. The preparations also modify dramatically the early febrile, toxic stage of the disease, causing a prompt fading of the rash and improvement in the patient's feeling of well-being.

What has been said for convalescent serum applies also to commercial antitoxin. Much more antitoxin can be given in an intramuscular injection of 3 to 5 cc. of the commercial preparations than in a transfusion of even 300 to 500 cc. of convalescent serum. But sensitization to horse serum and occasional reactions are encountered. Since the newer trypsin digest method of preparing the antitoxin has been used,

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26a. Rhoads, P. S.; Rosi, R., and Youmans, G. P.: Duration of Infection Following Scarlet Fever, Ann. Int. Med., to be published.

27. Observations on the Treatment of Scarlet Fever with Penicillin, Epidemiology Unit No. 82, United States Naval Hospital, Treasure Island, Am. J. M. Sc. **211**:417-420 (April) 1946.

28. Spink, W. W.; Rantz, L. A.; Boisvert, P. J., and Coggeshall, H.: Sulfadiazine and Penicillin for Hemolytic Streptococcus Infections of the Upper Respiratory Tract: Evaluation in Tonsillitis, Nasopharyngitis and Scarlet Fever, Arch. Int. Med. **77**:260-294 (March) 1946.

29. Rhoads, P. S., and Gasul, B. M.: Convalescent Scarlet Fever Serum and Commercial Antitoxin: A Comparison of Their Protective Values, J. A. M. A. **102**:2005-2008 (June 18) 1934.

late serum reactions have not occurred in more than 5 per cent of my cases, and these have been mild. Possibility of reaction, therefore, need not be a contraindication to its use except in persons shown to be highly sensitive to horse serum by the usual intraocular and intradermal tests.

Probably a combination of penicillin with convalescent serum constitutes the best treatment that can be given, if enough convalescent serum is administered. Penicillin together with antitoxin is equally effective and more easily obtainable, but its use is followed occasionally by serum sickness.

SUMMARY

In the present state of knowledge, the Dick method of five doses of scarlet fever streptococcus toxin U. S. P. totaling about 150,000 skin test doses, which has been proved over a period of years to give lasting immunity against scarlet fever, should be used for active immunization.

Since in past years none of the methods offered as a substitute for the Dick procedure has produced adequate and lasting immunity, the substitutes now available should be used with caution until their efficacy has been proved.

In the treatment of scarlet fever a combination of scarlet fever convalescent serum or antitoxin in full doses with penicillin seems to give the best results.

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News and Comment

GENERAL NEWS

Postgraduate Center for Psychotherapy, Inc., Offers Training Courses.—The Postgraduate Center for Psychotherapy, Inc., the training associate of the Institute for Research in Psychotherapy, Inc., has been granted a provisional charter from the Board of Regents of the New York State Educational Department. It offers intensive training for psychiatrists in psychotherapy leading to certification, and individual courses for general practitioners and nonpsychiatric medical specialists in psychotherapy and psychosomatic medicine.

Clinical psychologists and psychiatric case workers are trained in methods that are within the scope of their education and skills, and which can contribute to an integrated program. The primary aim of the program is to encourage the development of teams of psychiatrists, psychologists and social workers who can organize and operate community psychiatric clinics.

The courses of instruction include practical demonstrations in psychotherapy, as well as lectures. The work of all students is supervised by teachers qualified to manage a specific type of problem. Before the psychiatric student completes his training, he has had personal experience under supervision in the management of various types of cases.

There are required and optional lecture courses. Courses include the principles and practice of psychotherapy, psychodynamics and psychopathology, short term psychotherapy utilizing psychobiologic and psychoanalytic approaches, hypnotherapy, narcosynthesis, shock therapy, group therapy, case work therapy, psychologic counseling, child and adolescent psychotherapy, case conferences and seminars, organization and operation of a community psychiatric clinic, projective technics in psychotherapy, seminars on psychosomatic medicine, therapy of the neuroses and psychoses, compensation and medicolegal problems in psychiatry, anthropologic and sociologic aspects of psychiatry and industrial psychiatry.

Therapeutic Program.—The Institute, in close cooperation with the Postgraduate Center, also will carry out a therapeutic program. This contemplated activity will consist of the extension of clinic services to those who are in need of psychiatric treatment and unable to afford the fees of private psychiatrists.

Research.—A research program is in process to study and to evaluate all existing types of psychotherapy in order to determine their values and limitations, the kinds of patients benefited and the extent and quality of the successes achieved. The aims are to shorten treatment methods and to render them more efficient.

Public Educational Program.—The educational program is conducted in several channels; for the lay public, the general practitioner, the specialist in other branches of medicine and the psychiatrist. It is coordinated with the activities of existing agencies which are working in the same field.

Further information concerning this program may be obtained by writing to Stephen P. Jewett, M.D., Dean, or to Miss Janice Hatcher, Registrar, Postgraduate Center for Psychotherapy, Inc., 218 East Seventieth Street, New York 21.

Fellowships with Rochester Child Health Institute Available.—The Rochester Child Health Institute, Rochester, Minn., has arranged for two fellowships, recipients of which will be called Assistants of the Institute. These assistantships last for one year, one beginning January 1, and one July 1, each year. The service is in preventive medicine in pediatrics and facilities, including prenatal, newborn, infant, preschool and school care.

Considerable emphasis is placed on psychiatric, psychologic, developmental and nutritional, as well as the more purely medical, supervision. The service can be arranged to allow time for research activities. The American Board of Pediatrics gives credit for one year for training on this service.

A stipend can be arranged for, ranging from $1,600 up to $3,600, according to previous training and dependents of applicant. Preference will be given to those anticipating teaching as their final goal.

Applications will be sent on request and should be submitted not later than nine months prior to beginning of service, to Dr. Edith Hewitt, Chairman, Admissions Committee, Rochester Child Health Institute, City Hall, Rochester, Minn.

Rochester Child Health Institute Announces Assistantships.—The Rochester Child Health Institute, Rochester, Minn., announces two assistantships of one year each, one beginning January 1 and one July 1 of each year.

These services include preventive medicine in pediatrics, with the opportunity for study of normal growth and development, care of the newborn, well child care, psychologic problems in young children and school examinations. These are equivalent to fellowships in the sense that opportunities for both service and research are given.

The stipend of $1,620 is offered to suitable candidates. The first available fellowship will begin Jan. 1, 1950.

University of Arkansas School of Medicine to Give Postgraduate Course in Pediatrics.—There will be a postgraduate course in pediatrics given by the Department of Pediatrics, University of Arkansas School of Medicine, at the University Medical School, Little Rock, Ark., from 9 a. m., March 11, to 5 p. m., March 12, 1949. Topics of practical importance to practitioners will be discussed. Guest speakers will be Dr. James G. Hughes, associate professor of pediatrics, University of Tennessee, Memphis, Tenn., and Dr. Myron E. Wegman, professor of pediatrics, Louisiana State University, New Orleans. Physicians who are interested are invited to attend and to notify Dr. William A. Reilly, University of Arkansas School of Medicine, Little Rock, Ark.

Oral Examinations of American Board of Pediatrics, Inc.—The American Board of Pediatrics, Inc. will hold oral examinations in St. Louis on Feb. 18, 19 and 20, 1949, and in Baltimore, May 7, 8 and 9, 1949. This was changed from the previously published dates of April 22, 23 and 24, 1948.

Abstracts from Current Literature

Chronic Infectious Diseases

TYPES OF TUBERCULOUS DISEASE IN CHILDHOOD. T. VALLEDOR, C. HERNÁNDEZ MIYARES, A. FERNANDEZ BALTRONS, A. DE FERIA and J. CORNEJO, Rev. cubana de pediat. **18**:527 (Sept.) 1946.

The authors give a complete review of a large series of patients seen in the dispensary from 1939 to 1944. The Mantoux (intracutaneous) test was performed on 6,618 patients, from newborn infants to 13 year old children. Of these, 1,477 (22.3 per cent) were positive reactors. Tests on the negative reactors were carried out every six months, and 32 became positive, allowing the authors to analyze the onset of the primary infection in these patients.

In the first two years of life the primary and the postprimary are the most important forms of the disease. The intrathoracic infections are divided into four types on the basis of symptoms: (1) subclinical, or florid; (2) infections with general symptoms predominating (masked forms—dyspeptic, anemic and dystrophic febrile); (3) infections with definite physical signs (infiltrations, epituberculous and atelectatic lesions), and (4) infectious functional symptoms predominating (adenopathies, gangliobronchial fistulas). The extrathoracic types are classified as (1) discrete, disseminated (osteoarticular, ganglionic and cutaneous) and those considered a product of an allergic reaction (erythema nodosum, phlyctenular conjunctivitis) and (2) primary extrathoracic (cutaneous and mucosal; primary cervical and mesenteric adenitis).

After the age of 2 years there are three types of primary infection: (1) generalized adenopathy, in Negroes; (2) secondary infiltration of Redeker (regression perifocal reaction around lymph nodes), and (3) tertiary forms.

The following roentgenologic types are indicated: (1) single nodule (discrete primary complex), (2) perifocal reactions (epituberculosis), (3) type with atelectasis predominating, (4) primary complex with discrete dissemination, (5) tracheobronchial adenopathy, (6) pleural lesions and (7) residual lesions.

The authors believe strongly that vaccination with BCG, which produces an attenuated reaction, is preferable to the appearance of a natural infection, with all its contingencies

KEITH, Rochester, Minn.

TUBERCULIN TESTS OF SCHOOL CHILDREN. L. VARGA and S. M. KOVÁCS, Orvosok lapja **1**:373 (Nov.) 1945.

Comparative reactions to the Pirquet, Moro and Mantoux tests for tuberculosis showed that the most sensitive is the Mantoux test, which is easily performed and harmless. The Mantoux test therefore is the most advisable for tuberculin testing of school children. The authors used the Mantoux test, according to the directions of the Public Health Institute in Budapest, Hungary, in two dilutions: First, the children were tested with 0.01 mg. of tuberculin. Second, those with negative reactions were retested with 1 mg. tuberculin. This procedure gives exact results, and all infected children can be detected.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

TUBERCULOSIS IN 347 HOSPITALIZED CHILDREN. M. JACCOTTET and M. NICOD, Ann. pædiat. **167**:141 (Sept.) 1946.

After studying the histories of 347 tuberculous children, the authors conclude that tuberculosis spreads chiefly within the family. Social status, housing conditions, habits of life, constitution and state of health do not seem to exert any important influence on the prevalence of tuberculosis, except on the way in which the disease may develop. The importance which other authors attach to the school as a source of spread cannot be acknowledged. The transition to the secondary stage occurs most frequently when the children were primarily infected as infants. It is then that the mortality is greatest. Of the hospitalized children 88.8 per cent were cured clinically and 12.1 per cent died from tuberculosis, chiefly from the meningitic form of miliary generalization. Within the first eighteen months after primary infection the danger of spread is greatest. This interval gives a useful time limit in which to advise removal to high altitudes. Isolation and treatment in a sanatorium are the basis of prophylaxis and therapy.

FROM THE AUTHORS' SUMMARY.

Diseases of the Blood, Heart and Blood Vessels and Spleen

HYPERCHROMIC ANEMIA PRODUCED BY CHOLINE OR ACETYLCHOLINE AND THE INDUCED REMISSION OF BOTH BY FOLIC ACID OR LIVER INJECTION: THE PROBABLE MECHANISM OF ACTION OF LIVER AND FOLIC ACID IN TREATMENT OF ANEMIA. JOHN EMERSON DAVIS, Am. J. Physiol. **147**:404 (Oct.) 1946.

The author was able to produce significant hyperchromic anemia in 5 dogs by the subcutaneous injection of 3 mg. of acetylcholine bromide twice daily. He gave 2 animals 1 mg. of physostigmine salicylate to reenforce each dose of acetylcholine. Three other dogs received 200 mg. of choline chloride twice daily by oral administration; in them, too, anemia developed.

When folic acid was administered daily to 1 dog with anemia induced with acetylcholine and to 2 dogs with anemia induced with choline, a remission of the anemia was produced, and it was accompanied with early reticulocyte responses in spite of continued administration of acetylcholine or choline.

When liver extract was injected daily in 2 dogs with anemia produced by acetylcholine and in 1 dog with anemia induced with choline, reticulocytosis was produced, and a therapeutic remission of the anemias occurred in spite of continued administration of the anemia-producing agents.

From this observation, the conclusion is drawn that the important action of either folic acid or liver extract in the treatment of anemia is to increase the cholinesterase activity in the body.

STOESSER, Minneapolis.

THE SURGICAL TREATMENT OF CONGENITAL PULMONIC STENOSIS. ALFRED BLALOCK, Ann. Surg. **124**:879 (Nov.) 1946.

The main indication for surgical intervention in a case of congenital pulmonic stenosis is evidence of an inadequate flow of blood to the lungs. Important in the diagnosis are the absence of visible pulsations in the pulmonary fields, as observed under the fluoroscope, and roentgenographic evidence that the pulmonary artery is small. The author expresses the opinion that the most desirable age for surgical treatment of congenital pulmonic stenosis is from 2 to 10 years.

Operation was performed on a total of 110 patients. Either anastomosis between the end of a systemic vessel and the side of one of the two pulmonary

arteries or an end to end anastomosis was made. The subclavian artery was used in 46 patients; the innominate artery in 36 patients, and the carotid artery in 9 patients. In 10 patients anastomosis was attempted between the end of a systemic artery and the end of one of the two pulmonary arteries. In 3 patients a mistaken vessel was anastomosed, and in 6 patients anastomosis was not performed. The over-all mortality rate was 23 per cent.

BANTIN, Omaha.

THE HYPOXIA TOLERANCE TEST OF THE HEART IN CHILDREN. E. MANNHEIMER, J. Pediat. **29**:329 (Sept.) 1946.

In attempting better to evaluate the function of the heart in children, the author has developed a clinically practical test of hypoxia tolerance. While the patient is breathing 9 per cent oxygen for ten minutes and thereafter as he breathes room air, electrocardiographic and phonocardiographic tracings are made. The author's results with this procedure on 30 normal children and on 54 children with various types of congenital and acquired heart disease are presented.

GRULEE JR., Minneapolis.

HENOCH'S PURPURA: SMALL INTESTINAL CHANGES: CASE REPORT. W. H. WHITMORE and G. M. PETERSON, Radiology **46**:373 (April) 1946.

The authors direct attention to irregularity and dilatation of the terminal part of the duodenum and the first part of the jejunum in a man 20 years of age with nonthrombopenic (Henoch's) purpura. The mucosal outline resembled small diverticulums or ulcers. The authors suggest that roentgenographic studies of the small bowel may be of diagnostic aid in obscure conditions involving the abdomen.

ANSPACH, Chicago.

REFRACTORY ANAEMIA. DONALD PATERSON, Proc. Roy. Soc. Med. **39**:132 (Jan.) 1946.

The author reports the case of a girl 6 months of age with refractory anemia. The history, clinical observations, results of complete blood studies and a record of her progress in the hospital accompany the report.

WILLIAMSON, New Orleans.

TWO CASES OF BANTI'S SYNDROME: HEPATOMEGALY WITH ANAEMIA. CHARLES PINCKNEY, Proc. Roy. Soc. Med. **39**:134 (Jan.) 1946.

The author reports cases of Banti's syndrome (hepatomegaly with anemia) in 2 children of the same family. One child was 8 years of age, and the other was 3 years old.

WILLIAMSON, New Orleans.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

MESENTERIC BANDS PRODUCING INTESTINAL OBSTRUCTION IN A THREE-DAY-OLD INFANT WITH RECOVERY. A. R. SCHWARTZ, Arch. Pediat. **63**:317 (July) 1946.

A case history is presented in which a congenital adhesion caused intestinal obstruction at the level of the sigmoid portion of the colon. The adhesion was divided and continuity of the bowel established. A barium sulfate enema aided in the diagnosis.

A short review of the literature is presented, and methods aiding in diagnosis are discussed.

DAVIS, Denver.

CONGENITAL HEMANGIOMA OF THE PAROTID GLAND. KURT GLASER, W. HARRISON MEHN and LOUIS W. SCHULTZ, J. Pediat. **28**:729 (June) 1946.

A rare tumor of the parotid gland, the hemangioma, or hemangioendothelioma, which occurs in newborn infants, is described. The main diagnostic features are, appearance in early life, unilateral occurrence, enlargement of the tumor when the infant cries, elastic consistency and compressibility and evidence of lobulation on palpitation. The slow growth of this—technically speaking—benign tumor may change into a very rapid one, either spontaneously, without any apparent external stimulus, or on the occasion of taking a biopsy specimen. This rapid growth leads to invasion and compression of the vital organs of the neck and the early death of the patient.

The treatment suggested is the radical surgical removal of the tumor, without attempt to conserve the facial nerve or larger parts of the gland, followed by radiation therapy. The report of a case, with photomicrographs, is part of the article, and reference is made to an earlier paper by Glaser, with a complete review of the literature.

FROM THE AUTHORS' ABSTRACT.

A NEW CONCEPTION OF DIAPHRAGMATIC HERNIA. WILLIAM LINTZ, M. Rec. **159**:25 (Jan.) 1946.

The cardiac symptoms in large diaphragmatic hernia may be explained on the basis of pressure of the hernia on adjacent organs and blood vessels. The same symptoms associated with small hernias are due to a disruption of the relation of the negative thoracic pressure with the positive abdominal pressure which normally exists. The author gives substantiating evidence for his opinion, a case report and a technic for roentgenographic examination to increase the accuracy of diagnosis.

FERDINAND, Peoria, Ill.

ACUTE DIARRHEA IN CHILDREN. JAMES WATT and MARGARET F. GUTELIUS, New Orleans M. & S. J. **99**:266 (Dec.) 1946.

Diarrheal disorders constitute an important problem in the summer months, especially in the southern states. Clinical observations usually only suggest the etiologic agent. Accurate diagnosis is a laboratory problem. The pathogen is usually of the Shigella or the Salmonella group. The best medium for the purpose of differentiation is SS (Shigella-Salmonella) agar. The Shigella infections are susceptible to therapy with sulfonamide drugs, while the Salmonella infections are not.

Dehydration and acidosis constitute the major problems of treatment. If possible, the carbon dioxide–combining power of the blood should be obtained. Assuming that 55 volumes per cent is normal, sufficient one-sixth molar sodium lactate or 1.5 per cent sodium bicarbonate should be given to raise the carbon dioxide–combining power to this point. One cubic centimeter per pound (2 cc. per kilogram) of body weight of either solution is needed to raise the carbon dioxide–combining power 1 volume per cent. At least half the required amount should be given at once intravenously and the remainder subcutaneously or intraperitoneally. Dehydration is further combated by using Ringer's solution U. S. P. and 6 per cent dextrose in equal quantities. These may be given subcutaneously or intravenously. In cases of severe dehydration and acidosis 75 to 150 cc. of fluid per pound (150 to 300 cc. per kilogram) of body weight should be given in the first twenty-four hours. If given intravenously, one-half the amount is allowed to flow by gravity and the remainder at the rate of 5 to 10

drops per minute. If the drip method cannot be used, 10 to 30 cc. per pound (20 to 60 cc. per kilogram) may be given in a twenty to thirty minute period and repeated every four hours.

If the carbon dioxide determination is not available, it is advised that 15 cc. per pound of one-sixth molar sodium lactate or 1.5 per cent sodium bicarbonate be given intravenously, followed by an equal amount subcutaneously.

After fluid and electrolyte balance had been obtained, 60 cc. of fluid per pound of body weight will maintain hydration unless the diarrhea persists, in which event more will be required, and 15 cc. of one-sixth molar sodium lactate per pound of body weight will be required to prevent the recurrence of acidosis. Ketosis may be avoided by adding 0.5 Gm. of dextrose per pound of body weight each day.

In some cases the diarrhea fails to respond to this form of treatment. In such cases the causative factor may be a lack of potassium, as suggested by the work of Darrow.

In cases of moderate dehydration, lactated Ringer's solution U. S. P. is the choice of the authors. This may be given parenterally or by mouth if not vomited.

After body fluids have been restored, whole blood, plasma or amino acids may be indicated. Parenteral administration of vitamins is also advised.

Since the sulfonamide drugs are effective in treatment of Shigella infections and many cases are of this type, some sulfonamide compound may be given before the final diagnosis is established. Sulfadiazine is the choice recommended. The dose is ¼ to 1 grain (0.048 to 0.065 Gm.) per pound of body weight. The drug is continued until two negative cultures of the stool have been obtained, or for seven days, whichever is first.

The Salmonella infections do not respond to sulfonamide therapy, and proof that the infection is of that group indicates discontinuance of the drug.

General measures include rest, a fast of twelve to twenty-four hours and proper diet, and sedation if indicated. The diet should be low in carbohydrate and high in protein. Skimmed or evaporated milk is advised. Protein hydrolysates and protein milk may be valuable, especially early in treatment. Lactated Ringer's solution may be used as a milk diluent to prevent acidosis. The use of apple powders, foods combined with agar and kaolin have met with varied success.

BERKLEY, Beverly Hills, Calif.

CONGENITAL MEGACOLON TREATED WITH MASSIVE DOSES OF SYNTROPAN. VINCENT DEPAUL LARKIN and ADOLPH G. DESANCTIS, New York State J. Med. **45**:310 (Feb. 1) 1945.

The authors present a case of congenital megacolon in a 2 year old boy who responded well to the use of amprotropine phosphate N. N. R. ("syntropan"). For more than three weeks the patient received over 1,200 mg. of the drug in divided doses daily without any evidence of toxicity. Neostigmine bromide U. S. P. ("prostigmin bromide") and methacholine chloride U. S. P. ("mecholyl chloride") had failed to produce any benefit.

AIKMAN, Rochester, N. Y.

EFFECT OF SULFATHALIDINE AND SULFAMETHAZINE ON GASEOUS DISTENTION IN THE OBSTRUCTED SMALL INTESTINE OF CATS. ARNOLD SEGEL, FRITZ SCHWEINBURG and JACOB FINE, Proc. Soc. Exper. Biol. & Med. **63**:17 (Oct.) 1946.

The authors state that the three sources of gas in intestinal distention are air, decomposed food and diffusion of nitrogen from the blood into the intestine.

Forty-six cats were studied after being deprived of food and water for twenty-four hours. The esophagus was closed by stuffing with cotton, and the ileum was occluded at the ileocecal junction. Malted milk (100 cc.), which is a rich source of gas in the intestinal tract, was injected into the stomach, and "sulfathalidine" (phthalylsulfathiazole) or "sulfamethazine" (N'-[4,6-dimethyl-2-pyrimidyl] sulfanilamide), 0.1 Gm. per kilogram of body weight, was added to the malted milk of some of the animals. At the end of twenty-four hours the gas in the obstructed loop was aspirated. In the 16 control animals, gas production ranged from 30 to 200 cc. (average, 112.9 cc.); in the 20 animals treated with "sulfathalidine," from 0 to 60 cc. (average, 17.6 cc.), and in the 10 animals treated with "sulfamethazine," from 0 to 30 cc. (average, 12.0 cc.). The authors conclude that gas formation from malted milk in the gastrointestinal tract is depressed significantly by the drugs studied.

HANSEN, Galveston, Texas.

ROENTGEN CHANGES ASSOCIATED WITH PANCREATIC INSUFFICIENCY IN EARLY LIFE. EDWARD B. D. NEUHAUSER, Radiology **46**:319 (April) 1946.

From experience with 50 cases, the author reports on the roentgenologic aspects of pancreatic insufficiency. In the lung, peribronchial areas of pneumonia, frequent bronchiectatic abscesses and areas of displacement of connective tissue were common. Either nutritional failure or chronic pulmonary disturbances dominated the clinical picture. In meconium ileus, which is due to hypochylia or achylia, a diagnosis of intestinal obstruction was the only one possible for the majority of patients. Invariably associated with the nutritional disturbances was a chronic, severe bronchial obstruction, with eventually a superimposed staphylococcic infection.

ANSPACH, Chicago.

Nervous Diseases

TREATMENT OF PURULENT INFANTILE MENINGITIS. MARIO J. DEL CARRIL, FOLEY and PAZ, Arch. argent. de pediat. **25**:164 (March) 1946.

The authors report cases of pneumococcic and meningococcic meningitis successfully treated with penicillin and sulfamerazine U. S. P. They confirm the results of C. W. Cory and associates (*J. Pediat.* **25**:35-48 [July] 1944) and of Rosenberg and Arling (Penicillin in Treatment of Meningitis, *J. A. M. A.* **125**:1011-1017 [Aug. 12] 1944).

ROJAS, Boston.

TREATMENT OF HEMOPHILUS INFLUENZAE MENINGITIS. SALVADOR DE MAJO, C. PIANTONI and F. E. TORRES, Arch. argent. de pediat. **25**:339 (May) 1946.

The increase in frequency of Hemophilus influenzae meningitis is an evident phenomenon. Numerous articles from both foreign and national sources support this fact.

In following the procedure devised by Dr. Hattie E. Alexander, of Columbia University, New York, the authors successfully treated 71.4 per cent of patients (7 cases are included in the report). The only difficulty was the unavailability of anti-influenza rabbit serum.

This method of treatment is superior to those formerly used. Treatment is based on:

1. Intravenous administration of 10 per cent dextrose solution by the drip method, 20 cc. per kilogram of body weight during the first sixteen hours, then 5 cc. per kilogram per hour

2. Maintenance of an adequate sulfadiazine concentration in the spinal fluid
3. Treatment with sulfadiazine for at least fifteen days after the disappearance of the fever and the return of the spinal fluid to normal

ROJAS, Boston.

HEMOPHILUS INFLUENZAE MENINGITIS TREATED WITH PENICILLIN AND SULFADIAZINE. F. SCHWEIZER, N. SCATAMACCHIA, C. SCHWEIZER and A. VILLALBA, Arch. argent. de pediat. **25**:352 (May) 1946.

Four cases of Hemophilus influenzae meningitis successfully treated are reported. The best route of administration for penicillin was intrathecally. The concentration of the penicillin solution was higher than that generally advised for intrathecal use, reaching 2,000 Oxford units per cubic centimeter, without any noticeable disturbance.

The authors express the belief that penicillin must be administered intrathecally even after the return of the spinal fluid to normal.

ROJAS, Boston.

EFFECT AND THERAPEUTIC USE OF "NIRVANOL" (PHENYLETHYL HYDANTOIN). G. PETÉNYI, Orvosok lapja **2**:593 (May) 1946.

In cases of chorea minor the well known drug phenylethyl hydantoin ("nirvanol") was used. It was given until drug sickness developed. After these toxic effects disappeared, the chorea minor ceased for the most part, but in some cases phenylethyl hydantoin sickness was of such severe nature that the physicians did not dare expose the children to the effect of treatment with the drug. Petényi suggests that "nirvanol" be given in a daily dose of 0.30 Gm. increasing every second day until the quantity of the drug reaches 1.5 Gm. With this procedure a mitigated phenylethyl hydantoin sickness can be produced which is not at all harmful, and the chorea heals in 70 per cent of cases.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

PRIMARY PURULENT PYOCYANEUS MENINGITIS IN THE YOUNG CHILD. MIRA AGULNIK, Ann. pædiat. **167**:38 (July) 1946.

A case of pyocyaneus meningitis in a young infant, originating from a circumcision wound, is reported. The patient was treated with sulfonamide compounds. Administration of penicillin and lumbar puncture proved unsuccessful. This form of meningitis in early infancy is rare.

FROM THE AUTHOR'S SUMMARY.

SUBACUTE JUVENILE FORM OF FAMILIAL DIFFUSE CEREBRAL SCLEROSIS (TYPE SCHOLZ). C. DE LANGE, Ann. pædiat. **167**:169 (Oct.) 1946.

Some years ago the author reported in this periodical the history of a family in which 4 infants had died of diffuse sclerosis of the brain (type Krabbe). A postmortem examination and a histologic study of the brain were possible in 2 of them. She now gives the history of a family in which 2 of the children died of the juvenile form of the same hereditary disease (type Scholz). In 1 of them postmortem and histologic examinations of the brain could be made.

The clinical and histologic differences between the two types are discussed. On the basis of these two studies, the author states the opinion that the dysfunction of the neuroglia is the cause of the disease and not the demyelination of the nerve fibers, the latter condition being secondary.

FROM THE AUTHOR'S SUMMARY.

CHRONIC ALLERGIC MENINGITIS. HANS ZELLWEGER, Helvet. pediat. acta **1**:417 (July) 1946.

Three cases of chronic allergic meningitis with paralysis of cerebral nerves observed in children are described. From the many forms of idiopathic benign mononuclear meningitis, three chronic courses are differentiated: (1) chronic mononuclear meningitis with a high initial fever, partly relapsing, with severe meningismus and sporadic cerebral symptoms, such as pyramid tract signs, anisocoria and convulsions; (2) chronic rheumatic and neuralgiform disorders without meningitic signs (spinal puncture reveals only the presence of meningitis), and (3) chronic allergic meningitis with paralysis of the cerebral nerves and insignificant, or even no, meningismus.

FROM THE AUTHOR'S SUMMARY.

Psychology and Psychiatry

IMPULSIVE OUTBREAKS IN CHILDREN. ALFRED GORDON, M. Rec. **159**:537 (Sept.) 1946.

The author describes a variety of impulsive outbreaks from his observation of 37 children of all ages. The described "fugues" are manifested by unusual behavior, such as repeated running away from home for no apparent reason, or at least for reasons not sufficient to produce such an outbreak in the normal child. These children should be considered abnormal, although no other abnormal mental manifestation exists. Management of the child and advice to the parents should be directed along such lines if the children are to be guided safely to adult life to become useful members of the community.

FERDINAND, Peoria, Ill.

PSYCHOPATHIC INDIVIDUALITIES IN CHILDHOOD. BERNARDO SEREBRINSKY, Arch. argent. de pediat. **25**:219 (April) 1946.

The term individuality is used instead of the more usual personality in order that the latter term may express the biopsychic figure of a person who seeks complete social adjustment.

The clinical aspects of the following psychopathic individualities are described: the irregular psychopathic, the hyperemotive, the unstable and the asthenic-depressive individualities.

The fundamental feature of the first individuality is that the "same predominant symptom" is never presented. This condition must be thought of when a nervousness unexplained by any congenital or hereditary disease exists. This type of individuality must be treated by individual teaching, but not with isolation.

The second individuality includes extremely sensitive children who react out of proportion to internal or external stimuli. Obesity and exudative diathesis are frequently observed in these children.

In the unstable type, an uncontrollable necessity for movement is observed. The intelligence quotient is about 80. This individuality designates a permanent instability existing in the absence of organic lesions.

In the fourth type, children show from an early period a decided tendency to physical and mental fatigue. Diagnosis is easy when toxic or infectious astheniform processes, or endocrine disturbances capable of producing that picture, have been ruled out. The author doubts that the perverse type exists in the absence of any neurotic or neurologic process.

ROJAS, Boston.

Diseases of the Genitourinary Tract

ENDOMETRIOSIS IN YOUTH. JOHN FALLON, J. A. M. A. **131**:1405 (Aug. 24) 1946.

Although endometriosis is assumed to be extremely rare in youth, there were 9 girls in their teens with proved endometriosis among the last 225 patients who were seen in this (Fallon) clinic, an incidence of 4 per cent. The youngest girl was 13 years old.

It is suspected that the true incidence of endometriosis before the age of 20 years is greater than the percentage microscopically proved.

From the data obtained, the following conclusions seem valid:

1. Endometriosis should enter into the differential diagnosis of abdominal pain as soon as menstruation has been established. The cardinal symptom, as in older patients, seems to be increasing dysmenorrhea.

2. In women in whom the menstrual function has been established, whatever their age, appendectomy should be done through a median incision to allow light enough for inspection, not merely palpation, of the deep pelvis.

FROM THE AUTHOR'S SUMMARY.

A PRACTICAL URINE OR WET DIAPER SIGNAL. H. WRIGHT SEIGER, J. Pediat. **28**:733 (June) 1946.

Heretofore, all devices for use as urine or wet diaper signals have had one common fault. They have each consisted of two electric conductors separated with an absorbent nonconductor, which once it has been wetted becomes a conductor and has to be replaced or dried out before being used again. This fault makes the use of such a device complicated or requires the presence of many pads on hand, because they have to be washed and dried out before being used again.

The device to be described overcomes these disadvantages. In addition, it is so sensitive that wetting ½ square inch (16 sq. cm.) of the pad will cause a bell or other signal to be activated. Since the pad is made of rubber and metal only, it has no absorbent mediums and can be used indefinitely. In practice, a diaper is placed over the pad, or the diaper-covered buttocks rest on the pad. As soon as the wet diaper is lifted from the pad, the bell stops ringing. If there is a pool of urine on the pad, simply wiping it off with a dry end of the diaper makes the pad ready for use again immediately.

In addition to use as a signal of a wet diaper under an infant and for the older incontinent patient, it may be used in the study and treatment of enuresis, under a cystostomy opening and to detect leakage around the cystostomy or the cholecystostomy tube. Since all body fluids contain sufficient electrolyte to operate the device, other uses may suggest themselves.

The device has been made with a light signal instead of with a bell for cases in which a visual signal would be preferable to an auditory signal, as in a hospital.

The metal grid used in the device has been made of "inconel," a noncorroding nickel chrome alloy. This metal grid, which measures 4 by 6 inches (10 by 15 cm.) and is 0.006 inch (0.015 cm.) thick, is cemented to the rubber pad. To cause the metal grid to adhere to the rubber pad, a cement called "vulcalox" is satisfactory; after vulcanization in a mold, the metal is flush with the rubber, and the pad has a smooth over-all surface. The pad is ⅛ inch (0.3 cm.) thick in the center and tapers to a thin edge. At the periphery, the edges of the pad measure 12 by 18 inches (30 by 46 cm.). The pad is flexible and conforms readily to the contour of the body.

Further manufacturing specifications are as follows: The relay should be a simple one, of 500 ohms. A loud bell is provided when the pad is used in the treatment of enuresis. When the device is used as a wet diaper signal in the case of the small infant or the incontinent patient, a buzzer is perhaps more agreeable acoustically.

The current for the relay and the bell is supplied by six flashlight type D dry cells in series. While these cells have to be replaced oftener than the larger dry cells, their relative low cost and ease of replacement make them desirable. They also make a compact arrangement, and the customary intermittent use of the device enables these small cells to give many weeks of service before replacement is necessary.

FROM THE AUTHOR'S ABSTRACT.

THE DIAGNOSIS AND TREATMENT OF CYSTITIS IN WOMEN AND CHILDREN. HERMAN L. KRETSCHMER, New England J. Med. **233**:339 (Sept. 20) 1945.

Roentgenographic examination may precede or follow cystoscopic examination. The presence or absence of cystitis must be revealed by cystoscopic examination. If this shows nothing abnormal, it is reasonably certain that the patient does not have the disease, and further study to determine the cause of the symptoms is in order. Should this examination show the presence of an abnormality in the bladder, such as a stone, foreign body, tumor or ulcer, the appropriate treatment can be started at once. If on cystoscopic examination the bladder appears normal, as happens in a large number of persons, the upper part of the urinary tract must be investigated by means of ureteral catheterization. In many patients, the primary lesion is encountered in the kidney. Among the various lesions of the kidney which may be overlooked for a long time because of the presence of symptoms of cystitis is tuberculosis.

During the acute stages and the first attack of acute cystitis, it is important that the patient have complete rest in bed. The application of heat to the area of the bladder gives great relief, and hot applications to the suprapubic area are in order. The author does not use local treatment, such as instillations and irrigations, during the acute stages. The patient is made much more comfortable by thorough alkalinization of the urine. For this purpose the author prescribes potassium citrate and potassium acetate and small doses of sodium bicarbonate, for a week or ten days, at which time urinary antiseptics, such as methenamine U. S. P. ("urotropin"), are administered. It must be remembered that the urine must be acid during the administration of the methenamine. Most of the cases of so-called acute cystitis are self limited, and on this regimen the patient makes a complete recovery.

GENGENBACH, Denver.

Diseases of the Muscles, Bones, Joints and Lymph Glands

ILIAC LYMPHADENITIS IN CHILDHOOD. E. KERPEL-FRONIUS and G. KOCSIS, Ann. pædiat. **168**:15 (April) 1947.

Five cases of iliac lymphadenitis in childhood are described. The illness follows a primary infection, chiefly of the skin, and begins with a rise in temperature and pain in the hypogastrium and hip joint. Walking, standing and extension of the thigh are impossible on account of the spasm in the psoas muscle. Guarding in the hypogastric region often allows palpation of the gland only with use of an anesthetic. The differential diagnosis of this condition and osteomyelitis, coxitis and appendicitis is discussed. The seriousness of the illness is shown by the fact that of the 5 patients observed only 2 were cured by use of the sulfonamide com-

pounds alone. One of the other patients had a relapse; in a second the gland suppurated, and in the third the disease led to a severe staphylococcic septicemia. Penicillin had a prompt effect in all the cases.

FROM THE AUTHORS' ABSTRACT.

RECURRENT CONSTITUTIONAL INFANTILE PANMYELOPATHY (FANCONI). HANS ZELLWEGER and H. U. ZOLLINGER, Helvet. pediat. acta **1**:382 (July) 1946.

A sporadic case of infantile constitutional panmyelopathy (Fanconi) is reported. Pigmentation of the skin of the patient had existed since birth; later proportionate dwarfism, microcephaly and hypogonadism developed. When the patient was 12 years of age, there was increasing dysfunction of the bone marrow, mainly affecting erythropoiesis and thrombopoiesis, with consecutive anemia and hemorrhagic diathesis.

From the pathoanatomic point of view, the condition last mentioned is particularly striking, as it directly led to death through heart tamponade and total hemorrhagic permeation of the auricle. Signs of extensive decomposition of the blood (hemosiderosis and early diffuse cirrhosis of the liver) are interpreted as sequelae of the numerous organic hemorrhages. The bone marrow consisted almost wholly of fat marrow; regenerative processes were entirely missing, for which reason the change in the bone marrow is construed as hypoplasia.

There were osteosclerosis of the portion of the bone deposited by the connective tissue and periosteum and osteoporosis of that part formed by the endosteum.

The cause of the disease is a constitutional deficiency in the bone marrow.

FROM THE AUTHORS' SUMMARY.

THREE CASES OF OSTEOPSATHYROSIS IDIOPATHICA IN THREE GENERATIONS. TRYGVE KAHRS, Nord. med. (Norsk mag. f. lægevidensk.) **27**:1756 (Sept. 7) 1945.

The author reports 3 cases of the disease of Lobstein, 1 of them in a girl 4 years of age, the others in adults. Two of the patients showed a fully developed Eddowes' syndrome with brittle bones, blue scleras and deafness, while in the third patient only blue scleras and the disposition to fractures were established. A predominant hereditary trait could be demonstrated through three generations of the patients' families.

WALLGREN, Stockholm, Sweden.

CONGENITAL FRAGILITAS OSSIUM. P. A. NORDSTRÖM, Svenska läk.-tidning. **42**:974 (April 13) 1945.

During the last ten years the author has seen 8 patients with congenital fragilitas ossium, of whom 6 were boys. In 6 patients a hereditary trait was demonstrable. All had blue scleras. Fractures occurred for the first time at 15 months of age in 1 child and at 2 years of age in the others.

WALLGREN, Stockholm, Sweden.

PRIMARY CHRONIC INFECTIOUS POLYARTHRITIS AND SUBSEPSIS HYPERERGICA. J. L. KEYZER, Maandschr. v. kindergeneesk. **14**:145 (May) 1946.

A case of primary chronic infectious polyarthritis is described. A girl aged 3½ years was admitted to the hospital because of pain in the joints, a morbilliform exanthem, a high sedimentation rate, a systolic murmur in the heart and fever. Three years later she was again admitted for jaundice, with a high, intermittent fever. One month later inflammation of both knees with swelling and glomerulonephritis developed. Treatment with a gold compound gave good results.

The second patient, a boy aged 2½ years, had an exanthem with fever and a heart murmur. The heart was dilated to the left and to the right. After a few weeks he was discharged from the hospital, with a normal sedimentation rate, but a few months later he was again admitted, with fever and jaundice, and died. Blood cultures were sterile. Autopsy revealed acute degenerative hepatitis with jaundice, as well as fibrinous adhesive pleurisy and pericarditis. The author is of the opinion that the second patient had subsepsis hyperergica (Wissler).

VAN CREVELD, AMSTERDAM, NETHERLANDS.

Skin Diseases; Allergy

TREATMENT OF ASTHMA IN CHILDHOOD WITH LEVOROTATORY ASCORBIC ACID. P. MAYNADIER, Arch. franç. de pédiat. **3**:147, 1946.

Some success has been recently achieved in the management of asthma through the use of agents antagonistic to histamine. In discussing these remedies, Jean-Louis Parrot observed: "Antihistamine therapy seems irrational, since relief is obtained only during a crisis; it does not relieve pain and frequently is accompanied with vertigo, gastric distress and loss of appetite. Further research into the remote origin of asthma seems essential."

Haglesco of Bucharest, Hungary, in a monograph (1938) noted that examination of the urine during asthmatic attacks showed complete absence of ascorbic acid. Acting on this discovery, Haglesco was able to relieve many patients through injections of this substance. Some patients were reported as permanently cured.

With ascorbic acid no side reactions such as are universally observed with histamine are evident even when enormous doses are employed. It not only appears to relieve asthma in the crisis but acts to ameliorate the condition during the latent period. The mechanism of its action is not clear, but protection against anaphylactic shock must be considered. Vallery-Radot and Mauric (1942) studied the action of ascorbic acid on sensitized rabbits and observed no such protection; other investigators have seen abundant evidence of it. Polack asserted that the manifestations of asthma cannot be explained entirely on the theory of anaphylaxis and offers the theory that an endocrine factor, such as suprarenal insufficiency, may be concerned.

The parallelism of the latter disorder and ascorbic acid insufficiency is well known. The question arises whether the injection of ascorbic acid will suppress or attenuate the adrenal insufficiency.

The author has made numerous observations since 1940 on the use of ascorbic acid in bronchial asthma, choosing only those cases which have proved refractory to all other treatment through long periods. Intravenous injections were employed exclusively. Eleven of Maynadier's patients are reported on in full. In all instances in which the urinary index of this remedy approached that of a normal child of similar age, relief was prompt and permanent. He poses the question: Is asthma to be considered among the avitaminoses?

AMESSE, Denver.

TREATMENT OF ASTHMA IN CHILDHOOD WITH SHORT WAVES. I. RECHT, Orvosok lapja **1**:337 (Nov.) 1945.

Recht treated 40 asthmatic children with short waves and was well satisfied with his results. According to him, the results obtained with short wave therapy are better in childhood than in adult life.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

ANAPHYLACTIC REACTIONS TO MERCURIAL MEDICAMENTS IN CHILDREN, WITH SPECIAL REFERENCE TO MILD MERCUROUS CHLORIDE (CALOMEL) SICKNESS. G. FANCONI, A. BOTSZTEJN and P. SCHENKER, Helvet. paediat. acta **2**:3 (supp. 4) 1947.

A series of 59 cases of an anaphylactic reaction to mercury after the application of a mercury ointment and the internal administration of mild mercurous chloride (calomel) is reported. The local application of mercury may cause local or general exanthems and dermatitis, with or without a general febrile reaction.

Special attention is drawn to poisoning with mild mercurous chloride (39 cases), which generally occurred about the eighth day after administration. The drug was given usually in cases of intestinal parasitism. The chief symptoms were fever; pronounced polymorphic exanthems, the maculas being scarlatiniform in the first days but later becoming larger and irregular in shape; leukopenia with eosinophilia; general glandular swelling, and, sometimes, hypertrophy of the spleen. The course was generally benign. More serious complications, such as general and persistent dermatitis, spontaneous relapse, meningoencephalitis and agranulocytosis, may take place. The administration of mild mercurous chloride should thus be avoided in the treatment of intestinal parasitism.

Intoxication with mild mercurous chloride produces in the organism a change in the defense mechanism. An attack confers immunity in the majority of children; i.e., further administration of the drug does not produce recurrence of the disease. If treatment with mercury has been given previously, an accelerated reaction, similar to that in serum disease, may appear after administration of the mercurous chloride. At the climax of this disease the Bloch cutaneous test showed a positive reaction, but in the later stages the reaction remained positive in only a few cases. The clinical resemblance of poisoning with mild mercurous chloride to phenobarbital-phenylethylhydantoin intoxication is striking. The two conditions are allergic in nature.

The authors also describe cases of polyradiculoencephalitis and erythredema polyneuropathy (Feer's disease) which occurred as late neuroallergic reactions to the use of mercury. In 2 cases of lipid nephrosis due to mercury poisoning it was difficult to decide whether an allergic or a toxic reaction dominated.

FROM THE AUTHORS' ABSTRACT.

TWO CASES OF DERMATOMYOSITIS. GUNNAR AUKEN and ASGER LOUW, Nord. med. (Hospitalstid.) **28**:2369 (Nov. 9) 1945.

One case was that of an 8 year old girl who had become ill five to six weeks before admission to the hospital with swelling of the eyelids, which gradually affected the whole face and the extremities. Erythema, of the eyelids, cheeks, neck and radial sides of the arms soon appeared. Shortly before the patient was admitted, the general condition was affected, with pronounced fatigue and weakness. A decreased amount of serum albumin and creatinuria was demonstrated. Other laboratory examinations revealed nothing abnormal. Histologic examination of the skin and muscle tissue showed typical signs of dermatomyositis. The child was tentatively treated with vitamin E, with no definite improvement.

WALLGREN, Stockholm, Sweden.

FACTORS CAUSING SERUM SICKNESS. NILS FAXÉN, Svenska läk.-tidning. **42**:1506 (June 1) 1945.

The author presents an analysis of the incidence of serum sickness in 7,864 cases of diphtheria treated with serum. The author contends that the frequency of serum

sickness increases with the amount of serum injected and the increasing age of the patient and that it occurs more frequently in first-born children than in other children.

WALLGREN, Stockholm, Sweden.

ASTHMATIC ATTACKS IN CHILDHOOD. E. WINGE FLENSBORG, Ugesk. f. læger **107**:965 (Nov. 15) 1945.

The prognosis of asthma was studied in 298 children, aged 1 to 14 years, in 50 per cent of whom the disease had commenced before 3 years of age. The time of observation was at least five years. In 40.3 per cent the attacks had disappeared, generally at an age from 12 to 15 in the boys and 9 to 12 in girls. Of the children 54.7 per cent still had attacks, which had become worse in one tenth of them. None of the children had received any specific treatment. Five per cent of the children died, one third of them in status asthmaticus, the others from other diseases.

WALLGREN, Stockholm, Sweden.

Teeth and Dentistry

INHIBITION OF DENTAL CARIES BY INGESTION OF FLUORIDE VITAMIN TABLETS. LYON P. STREAN and JEAN P. BEAUDET, New York State J. Med. **45**:2183 (Oct. 15) 1945.

The suggestion is offered that there are factors apart from fluorine ingestion which aid in the prevention of dental caries. These other factors may be vitamins C and D, acting synergistically with fluorine. Fluorapatite may be adsorbed on the surfaces of tooth enamel and is resistant to bacterial decomposition and lactic-acid digestion. Fluorination of water is not practical, since the water intake varies with the individual person.

One tablet, containing 3 mg. of calcium fluoride, 30 mg. of ascorbic acid and 400 units of vitamin D as calciferol, was given daily without toxic effects and without mottling of enamel.

AIKMAN, Rochester, N. Y.

Miscellaneous

SYMPOSIUM ON THE PHARMACOLOGY OF DITHIOLS. J. Pharmacol. & Exper. Therap. (supp.) **87**:1 (Aug.) 1946.

A supplement to the August 1946 *Journal of Pharmacology and Experimental Therapeutics* is entitled "The Symposium on the Pharmacology of Dithiols." The biologic properties of the dithiols are published in the *British Biochemical Journal*, and the clinical application is presented in the *Journal of Clinical Investigation*. The dithiol chosen for study was 1-2 dimercaptopropanol, coded as BAL (British antilewisite). Lewisite (β-chlorovinyldichloroarsine) was the arsenical irritant developed in the United States during World War I. BAL, and related dithiols, have been found to be effective in the treatment of arsenic and mercury poisoning in man.

In the introduction to the papers which make up the study of BAL in animals, it is stated: "In the recommended dosage of 2.5 mg./Kg. of body weight at 4 hour intervals, given as a 10 per cent solution of BAL in oil by intra-muscular injection, there have been very few reactions and these are of a minor nature. Occasional patients complain of nausea, generalized aches and pains or a burning sensation in the mouth or eyes. The blood pressure is frequently raised and rarely there may

be a sense of constriction in the throat and chest. These symptoms do not last more than 30 to 60 minutes and no cumulative toxicity results from repeated injections at 4 hour intervals.

"BAL is effective by local application in decontaminating the skin and preventing the toxic effects of lewisite. By intra-muscular injections excellent results have been obtained in certain of the serious toxic reactions following mapharsen, especially toxic encephalopathy and dermatitis. However, it is of doubtful value in blood dyscrasias and jaundice due to arsenic. While difficult to evaluate, the results to date indicate that BAL is remarkably effective in mercury poisoning, all of a consecutive series of thirty patients having recovered under this treatment, some of whom otherwise would not have been expected to survive."

PILCHER, Cleveland.

DANIEL WHISTLER AND HIS CONTRIBUTION TO PEDIATRICS. H. P. TAIT, Edinburgh M. J. **63**:325 (June) 1946.

Almost three hundred years ago, Whistler presented a thesis with the first clear account of rickets, although Reusner, at Basel, had published a description of a disease common in Switzerland and the Netherlands that was obviously rickets. Reusner merely spoke of the disease as occurring in children who showed weakness of the arms and legs, with bowing thereof, and deformities of the chest. In England the word "rickets" began to be used about 1625; the word "rickety" first appeared in 1738.

Whistler read his thesis on rickets in 1645, and it was soon published in book form, in eighteen pages. He stated that the disease was known in England. He listed seventeen cardinal symptoms and signs, the first ten of which are still recognized as clinically present, the other seven not being cardinal symptoms. The essay by Whistler is weak in his lack of knowledge of the morbid anatomy of rickets, but his clinical description of the disease is worthy of the recognition that has been accorded him.

Of the copies of the edition published in 1645, one is in the library of the Royal College of Physicians in London and another in the British Museum.

NEFF, Kansas City, Mo.

ACUTE QUININE POISONING: REPORT OF A CASE. A. GALEOTTI FLORI, Riv. di clin. pediat. **41**:357 (June) 1943.

A boy 10 years of age had taken six tablets of quinine bisulfate, containing 0.2 Gm. each. The early symptoms were dizziness, hypothermia (temperature, 35.8 C.), vomiting, diarrhea and headache. The most disturbing and persistent symptoms and signs were referable to the eyes. There was loss of vision for about thirteen days and loss of the light reflex for sixteen days. Extreme mydriasis persisted for thirty days. Ophthalmoscopic examination revealed spasm of the retinal vessels, papilledema and, later, beginning optic atrophy. The treatment included papaverine and ergotamine tartrate U. S. P. ("gynergin") to combat the toxic sympatheticotonic action of the quinine.

HIGGINS, Boston.

TARTARIC ACID POISONING FROM A PURGATIVE LEMONADE. LELIO NASSI, Riv. di clin pediat. **43**:36, 1945.

A rare case of poisoning from tartaric acid in a purgative lemonade is described. The symptoms were principally those caused from renal block, with uremia, painful hepatomegaly and ulceration of the oral mucous membrane. The child, after a

transitory improvement following treatment with thyroxin U. S. P., theophylline U. S. P. and calcium gluconate U. S. P., died from an intercurrent infection which increased the uremia.

After reviewing the literature on this type of poisoning, the author describes the pathologic changes in rabbits experimentally poisoned and presents data which completely explain the symptoms observed in the patient.

In a clinical picture similar to the one described, the possibility of poisoning from tartaric acid or from other organic acids must be kept in mind, even when the history of the patient gives no indication.

FROM THE AUTHOR'S SUMMARY.

ACUTE ALCOHOL POISONING IN CHILDHOOD. F. GERLÓCZY, Orvosok lapja **2**:662 (June) 1946.

A boy 9 years of age drank 100 Gm. of brandy whose alcoholic content was 50 per cent. He soon lost consciousness without vomiting. The child was brought into the hospital one and a half hours later with convulsions, dyspnea and no pulse at all. Gastric lavage and cardiac stimulants cured the child, who was dismissed from the hospital the next day. A 50 Gm. dose of alcohol is enough to cause toxic symptoms even in adults. Death can be caused in adults by 50 to 200 Gm. Since the greater part of the alcohol was still in the stomach after one and a half hours, gastric lavage easily removed it.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

HEMATOLOGY OF MALIGNANT TUMORS IN CHILDHOOD. ROBERT F. LANDOLT, Helvet. pediat. acta **1**:403 (July) 1946.

In 47 cases of malignant tumors (mostly sarcoma and sympathogonioma) from the Children's Hospital in Zurich, the following hematologic observations were made: 1. The sedimentation reaction was strongly accelerated in almost all cases. 2. There were frequently considerable leukocytosis with displacement of the neutrophils to the left, a myeloid reaction (particularly with the sympathogoniomas which had metastasized to bone marrow), anemia and a more or less febrile course. A high degree of leukocytosis was particularly characteristic of adenomyosarcoma. 3. In the bone marrow an increase in the reticulum cells and displacement of leukopoiesis to the left could often be established. 4. In a case of reticulosarcoma, the sarcoma cells could be observed in the bone marrow and on smears of glandular and pleural exudate and from them a correct diagnosis established. (The close relation of reticulosarcoma and lymphogranulomatosis is noted.) 5. In 11 of 16 cases of sympathogonioma, the characteristic tumor cells were in the bone marrow, and definite diagnosis could be made in each case. The presence of macrophages was particularly typical, and macrophagic mitosis was observed for the first time. Puncture of the tumor gave unequivocal results and allowed a certain diagnosis in 2 other cases.

FROM THE AUTHOR'S SUMMARY.

Book Reviews

Skeletal Tuberculosis. By Vicente Sanchís Olmos, M.D. Translated from the Spanish by J. G. Kuhns. Price, $5. Pp. 261, with 104 illustrations. Baltimore: The Williams & Wilkins Company, 1948.

This book was written with the stated purpose of presenting new, or little known, facts concerning tuberculosis of bone. A large amount of material covering all phases of skeletal tuberculosis was studied in preparation of the treatise.

The book is subject to criticism for several reasons. First, the proof obviously was not carefully edited, for there are numerous misspelled words and typographic errors throughout the text. For example, on page 42 there are three misspelled words in lines 6 and 7. Second, although there are a few new ideas presented, the entire work is written in a terminology which is unfamiliar to the medical profession of this country. Terms, such as parallergic, hyperergy, anergic, anergy, paraspecific, local bud, partial local bud and general bud, are frequently used in a manner confusing to the ordinary student of the subject. The text would be more widely appreciated by the profession if the translation had included simplification into a more familiar terminology.

The illustrations are numerous and well chosen. The book is of value mainly for those who have a specific and direct interest in the subject of skeletal tuberculosis. Careful study of the text is necessary to appreciate fully the valuable material that it contains.

Paediatrics for Nurses. By Arthur G. Watkins, M.D., F.R.C.P. Price, $3.50. Pp. 192, with 22 illustrations. Baltimore: The Williams and Wilkins Company, 1948.

This brief little volume is a new book designed to introduce to the nurse the main problems and diseases of childhood with which she will have to deal later. It omits all nursing technic, and because other books on the subject are available no attempt is made to include the infectious diseases. As a book for nurses, therapeutics is briefly mentioned, this being considered the province of the physician.

The book is excellent and quite up-to-date so far as it goes. Dr. Watkins is an excellent writer and apparently an able pediatrician. It is to be regretted that he should choose to be so brief. The 184 pages of text are divided into 26 chapters, some of which are excessively short, as, for example, the 2½ pages devoted to skeletal disorders and a like space to venereal disease.

Aside from the deliberate brevity of the text, few faults are found. The illustrations, mainly photographs, are excellent, and the reproductions of roentgenograms are especially superior. The book will serve its stated purpose well and is recommended as a review for nurses.

Give Your Child a Chance. By Lenore Turner. With a preface by Donovan J. McCune, M.D. Price, $1.50. Pp. 170, with 8 illustrations. New York: Georgian Press, Inc., 1948.

This is another in the long series of books being published in an attempt to return to a common-sense basis of child rearing. It offers nothing new, but its brevity is to be commended. Virtually every phase of a child's mental development

is included, and the discussion is sensible throughout. A brief section on feeding is included, with emphasis on the essentials of a good diet and the development of good feeding habits.

The book does not add anything of importance to the field of child rearing. It is, however, good as far as it goes and would undoubtedly be of aid to a certain type of parent.

Essentials of Fevers. Second edition. By Gerald E. Breen, M.D. (N.U.L.DuB.), D.P.H., D.O.M.S. (R.C.S.); Temporary Divisional Officer, Hospital Division, the London County Council; Late Municipal Medical Representative and Deputy Sector Hospital Officer, Emergency Medical Service; Formerly Deputy Medical Superintendent, the London County Council Infectious Hospitals Service; Examiner in Fevers to the General Nursing Council of England and Wales. Price, $4.50. Pp. 351, with 17 color plates and 24 illustrations. Baltimore: The Williams & Wilkins Company, 1948.

This volume relates primarily to the infections usually spoken of in this country as the common contagious diseases. In the preface, mention is made that the book is bulkier by inclusion of new sections on typhus, infectious mononucleosis, brucellosis, influenza and epidemic encephalitis, as well as "notes" on sore throat and food poisoning. Nevertheless, there is nothing burdensome about the additions. The color plates referred to as an innovation are always of particular interest to the student, and the author should be proud of his work as an artist in producing them.

The first four chapters or "sections" concern the general features of infection, epidemiology and associated topics and examination and treatment of patients with fevers. There is an abundance of practical knowledge, which, unfortunately, will not be appreciated fully by most students until they have had some years of experience.

The subject matter is concise and conclusive in nearly every respect. Therefore, it is a little surprising that some lack of faith appears in the almost universally accepted belief that Hemophilus pertussis is the real etiologic factor in whooping cough. For a small book it is one of the best yet published on the acute infectious diseases. There are no references and few allusions to other writers, thus promoting brevity.

Viral and Rickettsial Infections of Man. Edited by Thomas M. Rivers, M.D. Price, $5. Pp. 587, with 77 illustrations, including 6 plates in color. Philadelphia: J. B. Lippincott Company, 1948.

This single volume, with articles contributed by 27 of the foremost virologists of our day, fills a most pressing need. The reader not only is supplied with general information concerning all aspects of the study of viruses and Rickettsia, from immunology to electron microscopy, but also is furnished succinct clinical descriptions of the diseases these organisms produce in human beings. In addition, diagnostic procedures of choice are defined wherever they are available, frequently with full descriptions of the technical steps involved, as, for example, the cold hemagglutinin test. In the reviewer's opinion, the editor has been singularly successful in attaining his stated goal of providing a book to which medical students and practicing physicians may turn for information. Such workers, as well as others with more special interests, will find it well organized, well written, well illustrated and well indexed. The complete bibliographies following each section are particularly attractive.

EMIC (Emergency Maternity and Infant Care): A Study of Administrative Experience. By Nathan Sinai, D.P.H., and Odin W. Anderson, Ph.D. Bureau of Public Health Economics. Research Series No. 3. Gratis. Pp. 180, with no illustrations. Ann Arbor, Mich.: University of Michigan School of Public Health, 1948.

The Emergency Maternity and Infant Care plan was the first national health plan which could be analyzed in detail. It offered an important field for the accumulation of information regarding governmental health programs. Full cooperation was available from the Children's Bureau of the United States Department of Labor.

The report covers the history of the EMIC program, from its inception, through the many changes made, to its final form. The major problems considered are those of organization and administration.

The authors regard several points as obvious. First, insufficient attention was paid to the details of administration. Even in the relatively restricted services offered under EMIC, this was shown repeatedly. Neither the Children's Bureau nor any other federal agency was prepared for an adequate administration. The same situation prevailed among state agencies.

A second lesson is that adequate time is required to prepare for a widespread distribution of health services. Two years, the authors feel, would be a minimum time for such preparation.

Third, the study seems to show that local administration gives the best results in a program that is to be understood by physicians, hospital administrators and the beneficiaries. Difficulties multiplied when administration was centralized.

Fourth, the consensus among those interviewed in the field indicated a strong preference for allowing each individual state to handle its own funds in its own way. The authors comment that grants-in-aid and state responsibility appear to be the best method, but not because such a program offers any less complexity of administration.

Difficulties were encountered in payment for physicians' services. It was soon found that whereas average fees in private practice varied in sections of the country, all states soon demanded the maximum allowed, and payments became uniform throughout the country. It is apparent that no national plan can set varying rates on a geographic basis. Nothing of value was learned regarding payment for specialists' services, other than that the subject is a difficult problem which must be studied in detail.

One gains the impression from this study that EMIC worked well in spite of immense difficulties because of cooperation among all participating groups. The experience should serve as a deterrent to any precipitate action to institute national health services.

Progress in Neurology and Psychiatry, 1948. Volume 3. Edited by E. A. Spiegel, M.D. and others. Price, $8. Pp. 661. New York: Grune & Stratton, Inc., 1948.

This annual review of neurology and psychiatry covers 2,800 papers, with predominant emphasis on neurology. For the pediatrician, the book has limited value because much more attention is given to the problems of adults than to those of children. However, the chapters on mental hygiene, child psychiatry, mental deficiency, the neuroses, psychosomatic medicine, group psychotherapy and psychoanalysis will be of interest and value for the physician working with children. The reviews making up these chapters have been arranged by physicians who are out-

standing in their fields. The reviews include descriptive summaries of recent advances in clinical medicine, discussion of trends in the care and investigation of the patient and numerous bibliographic references at the end of each chapter, which alone are worth the price of the book. The book suffers from overcondensation of some of the topics. However, when a contributor is faced with a subject of special interest to him, he "lets out," and, as a result, some of the reviews are well rounded short essays. An example of this is Bender's review of schizophrenia.

Strabismus, A Clinical Handbook. By George J. Epstein, M.D. Price, $5. Pp. 214, with 123 illustrations. Philadelphia: The Blakiston Company, 1948.

There are other books on the subject, but this one covers quite well the whole field of strabismus. Although intended for the ophthalmologist, much of the material will be understood by the pediatrician. A review of the anatomy and physiology of the extraocular muscles is followed by a treatment of the theories of binocular vision and of the etiology and pathogenesis of strabismus.

Practical clinical details as to measurements, treatment and surgical measures are given and well illustrated. In this complex field of much controversy and conflict of theories, the writer and publishers have put together a concise, practical and well printed book. It compares favorably with other writings in the field.

Invaginación intestinal en el niño. By Alberto Lagos García, M.D. No price given. Pp. 209, with 68 illustrations. Buenos Aires, Argentina: "El Ateneo," 1947.

This is a conscientious study of intestinal intussusception based on 529 cases occurring in 495 patients. There are chapters on the etiologic basis, pathologic modifications, symptoms, diagnosis and treatment of this condition.

Particularly extensive is the chapter dedicated to roentgenologic technics and findings, which is illustrated with many good pictures. The various operative technics are described in detail.

The book carries an extensive bibliography in several languages, including references to many American authors.

Psychiatric Examination of the School Child. By Muriel Barton Hall, M.D. Price, $4.50. Pp. 356, with no illustrations. Baltimore: The Williams & Wilkins Company, 1948.

This book apparently grew out of the reforms of the Education Act of 1944 in England, which provides for special schools and special provisions in ordinary schools for all children who, because of disability of mind or body, need special education. As the author says, "an attempt has been made to describe and discuss what happens at a clinic or outpatient department to which a child is sent for psychiatric opinion," and the present volume resulted from experience gained in a provincial area of England and Wales.

The major portion of the book is taken up with a rather comprehensive coverage of the problems faced by the psychiatrist who deals with school children.

The emphasis is on the examination, diagnosis and report for carrying out the "legal measures" provided by local educational authorities, such as "special education by special methods, for the less seriously handicapped children in the ordinary schools and for the more seriously handicapped in special schools. Treatment and "environmental adjustment" are only briefly considered and

outlined. More attention is given to providing advice to the parent, guardian, teacher or any other person concerned with the child's welfare. However, from the setting one may assume that the psychiatrist's function is quite limited and, for the most part, serves the local educational authority by defining the nature of the child's condition or disability and the advisability of education in an ordinary or special school or class. Another function is to advise the court.

The examination itself is divided into two parts. Part one is concerned with complaints and investigations, including history, examination and tests; part two covers the description of the findings, which are classified under the usual headings of disorders in mental development, physical disorders, temperamental states and nervous habits, personality and behavior disorders, juvenile delinquency, psychoneuroses, psychoses and psychopathic states, including brief case reports.

While the British with their Education Act of 1944 may attempt to meet all needs by requiring certain educational services for all handicapped children, the law would appear to place more responsibility on the authorities than they are prepared to carry out. Of course, the approach to these problems in the United States is spotty, but there seems to be a growing recognition here of the need for training pediatricians and child psychiatrists who will be concerned not only with classification and diagnosis, but with the prevention of mental ill health, treatment of existing mental disorders and guidance of parents and teachers for better mental health of children.

How Parents and Teachers Can Help Prevent Stuttering in Children: Eight Keys to Normal Speech. By Leon Lassers, State Department of Education, Salem, Ore. No price given. Pp. 64. Portland, Ore.: State Printing Department, 1947.

The general advice given by most speech clinics is presented in popular style for the use of parents, teachers and others. The article consists of the expansion of eight general principles in the prevention of stuttering:

1. Do not label your child a "stutterer" or his way of speaking as "stuttering." Accept his speech as a perfectly natural way for him to talk.

2. Do all you can to give your child a feeling of security, confidence and success. Make him feel that he is worthy and loved.

3. Try to make your child's home a calm, pleasant place, free of family quarrels, conflicts and tensions.

4. Give your child a chance to talk in the most favorable circumstances.

5. Try to make your child's school and classroom experiences happy, successful ones—relatively free of pressures and tensions.

6. A child may safely be trained in righthandedness from infancy, but, if left-handedness consistently asserts itself or has become fixed, seek the guidance of an expert.

7. Keep your child in the best possible physical condition.

8. Give adequate oral, aural and rhythmic stimulation. Use daily rhythm, rhyming and listening activities, sound play, speech games and conversation.

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

Sixth International Congress of Pediatrics

President: Prof. Guido Fanconi.
American Committee:
President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.
Place: Zurich, Switzerland. Time: July 24-28, 1950.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana, Cuba.

International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quay Wilson, Geneva, Switzerland.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Secção de Pediatrias

President: Dr. Armando de Arruda Sampaio.
First Secretary: Dr. Luis Fontoura y Lauro Machado Oliveira, Caixa Postal 2103, São Paulo, Brazil.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

British Paediatric Society

President: Dr. H. T. Ashby, 13 St. John St., Manchester, England.
Joint Secretary: Prof. Alan Moncrieff, Hospital for Sick Children, Great Ormond St., London W. C. 1.
Place: Windermere.

Chinese Pediatric Society

President: Dr. W. S. Fu, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Secretary: Dr. T. F. Su, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Time: Concurrent with the annual conference of the Chinese Medical Association.

Danish Pediatric Society

President: Prof. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjørup, Dronning Louises Børnehospital, Copenhagen.

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

NEDERLANDSCHE VEREENINGING VOOR KINDERGENEESKUNDE

President: Dr. J. L. Keyzer, 114 St. Josephstr., Tilburg.
Secretary: Dr. H. Reerkink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICANS OF CHILDREN'S DISEASES

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASES IN CHILDREN

President: Prof. J. M. Smellie, 5 Flat, 8 Bolingbroke Grove, London S. W. 11.
Secretary: Dr. Mary Wilmers; Dr. R. Bonham Carter.
Place: 1 Wimpole St., London W. 1. Time: Fourth Friday of each month, 4:15 p. m.

SCHWEIZERISCHE GESELLSCHAFT FÜR PÄDIATRIE

President: Prof. Dr. A. Hottinger, Petersplatz 12, Basel.
Secretary: Dr. F. Hauser, Kinderspital, Basel.

SOCIEDAD BOLIVIANA DE PEDIATRIA

President: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Secretary: Dr. Cecilio Abela Deheza, Bolivia.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

SOCIEDAD CHILENA DE PEDIATRIA

President: Mr. Raúl Matte, Santiago, Chile.
General Secretary: Dr. Mariano Latorre, Santiago, Chile.
Place: Medical Society, Santiago, Chile. Time: 7:30 p. m., weekly.

SOCIEDAD CUBANA DE PEDIATRIA

President: Prof. Agustin Castellanos.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: 9 p. m., last Wednesday of every month.

SOCIEDAD DOMINICANA DE PEDIATRIA

President: Dr. Alberto Peguero, Avenida Bolivar 117, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Jaime Jorge, Lea de Castro 19, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Friday of every month.

SOCIEDAD ECUATORIANA DE PEDIATRIA

President: Dr. Alfredo Ceballos Carrión.
Secretary: Dr. Rafael Compte Andrade, P. O. Box 3480, Guayaquil.
Place: Hospital Central. Time: 11:30 a. m., every Friday.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Jesus Avarez de los Cobos.
Secretary: Dr. Luis Torregrosa F.
Place: Hospital Infantil. Time: Last Thursday of every month.

SOCIEDAD DE PEDIATRÍA DE CONCEPCIÓN (CHILE)

President: Dr. Raúl Ortega A., Hospital Clínico Regional, Concepción.
Secretary: Dr. Fidel Urrutia, Hospital Clínico Regional, Concepción.
Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., second Tuesday of every month from April to December, inclusive.

SOCIEDAD DE PEDIATRÍA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Albino F. Dottori, Dean Fumes 2000, Esq. Ocaña (N.), Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Fumes 2000, Córdoba, Argentina.
Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pastor Oropeza, Caracas.
Secretary: Dr. Guillermo Flores, Chacin, Sur 17, no. 26-2, Caracas.
Place: Hospital Municipal de Niños, Caracas. Time: Once a month.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. José Lavalle, Yucatan, Mexico.
Secretary: Dr. Francisco Solís, Yucatan, Mexico.
Place: Hospital del Niño, Yucatan, Mexico.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7e, France.
Secretary: Dr. Maurice Lamy, 94 rue de Varenne, Paris 7e, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. Basil Melle, 89 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.
Secretary-Treasurer: Dr. Seymour Heymann, 17 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Dr. R. Hybbinette, Kommendorsgatan 3, Stockholm.
Secretary: Dr. B. Broman, Eriksbergsgatan 1A, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

URUGUAYAN SOCETY OF PEDIATRICS

President: Dr. Héctor C. Bazzano.
Secretary: Dr. José M. Portillo.
Place: Club Medico del Uruguay, Avenida Agraciada 1464 (Piso 13), Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Woodruff L. Crawford, 321 W. State St., Rockford, Ill.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.
Place: Atlantic City, N. J. Time: June 6-10, 1949.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Warren R. Sisson, 319 Longwood Ave., Boston 15.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Atlanta, Ga. Time: April 13-15, 1949.
Annual Meeting: Place: San Francisco. Time: Nov. 14-17, 1949.

AMERICAN HOSPITAL ASSOCIATION, MASSACHUSETTS HOSPITAL ASSOCIATION

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Valjean Cooke, 8700 Argyle Ave., St. Louis.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.
Place: Atlantic City. Time: May 3-5 (?), 1949.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. P. E. Williams, 193 James St. S., Hamilton, Ontario.
Secretary-Treasurer: Dr. R. L. Denton, 1615 Cedar Ave., Montreal.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Sidney Farber, 300 Longwood Ave., Boston.
Secretary: Dr. Robert Ward, Bellevue Hospital, New York 16.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Spencer Snow, 75 S. Main St., Salt Lake City.
Secretary-Treasurer: Dr. Esther Gross, 202 E. South Temple St., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. Howard W. Brayton, 179 Allyn Street, Hartford 3, Conn.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. Clarence L. Lyon, 407 Riverside Ave., Spokane 8, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. Paul Bancroft, 909 Sharp Bldg., Lincoln, Neb.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. William D. Rothwell Jr., Republic Bldg., Denver.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Children's Hospital of the Colorado General Hospital. Time: Monthly from October to June.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. Carroll M. Pounders, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5, Ala.
Secretary-Treasurer: Dr. D. B. Monsky, 905 Norman Bridge Rd., Montgomery 6, Ala.
Place: Montgomery, Ala. Time: September 1949.

ARIZONA PEDIATRIC SOCIETY

President: Dr. Hugh Thompson Jr., 110 S. Scott St., Tucson, Ariz.
Secretary: Dr. James R. Sickler, Physicians Bldg., Tucson, Ariz.
Place: Phoenix or Tucson. Time: On call.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS
Chairman: Dr. Alice Potter, 1418 Ninth Ave., San Francisco 22.
Secretary: Dr. Carl Erickson, 595 E. Colorado, Pasadena.
Place: Los Angeles. Time: April 1949.

FLORIDA STATE PEDIATRIC SOCIETY
President: Dr. Edgar W. Stephens, 910 Harvey Bldg., West Palm Beach.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

GEORGIA PEDIATRIC SOCIETY
President: Dr. Lee Bivings, 20 Fourth St. N. W., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT
President: Dr. H. L. F. Locke, 179 Allyn St., Hartford, Conn.
Secretary: Dr. L. W. Minor, 119 Main St., Middletown, Conn.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS
Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. George L. Drennen, Jacksonville, Ill.
Place: Palmer House, Chicago. Time: May 10-12, 1949.

INDIANA STATE PEDIATRIC SOCIETY
President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY
President: Dr. Charlotte Fisk, 1201 Equitable Bldg., Des Moines 9.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.
Place: Des Moines. Time: April 1949.

LOUISIANA STATE PEDIATRIC SOCIETY
President: Dr. William C. Rivenbank, 1448 Louisiana Ave., New Orleans 15.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.
Place: New Orleans. Time: May 7, 1949.

MEDICAL SOCIETY OF THE STATE OF NEW YORK, PEDIATRIC SOCIETY
Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION
Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION
Chairman: Dr. H. J. Lewis, 2956 Biddle Ave., Wyandotte.
Secretary: Dr. Robert H. Trimby, 122 W. Hillsdale, Lansing.

MISSISSIPPI STATE PEDIATRIC SOCIETY
President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Place, Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY
President: Dr. George Clark, 1817 Vinton St., Omaha.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: Children's Memorial Hospital. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW JERSEY MEDICAL SOCIETY, PEDIATRIC SECTION
Chairman: Dr. Robert E. Jennings, 117 Washington St., East Orange.
Secretary: Dr. Israel J. Wolf, 231 E. 31st St., Paterson.

NEW MEXICO STATE PEDIATRIC SOCIETY
President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

NORTH CAROLINA PEDIATRIC SOCIETY
President: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.
Secretary: Dr. Charles H. Gay, 1523 Elizabeth Ave., Charlotte, N. C.

NORTHERN CALIFORNIA PEDIATRIC SOCIETY
President: Dr. William C. Deamer, 3 Fifth Ave., San Francisco 18.
Secretary: Dr. A. L. Gleason, 1066 Longridge Rd., Oakland 10.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

OKLAHOMA STATE PEDIATRIC SOCIETY
President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

PHILIPPINE PEDIATRIC SOCIETY
President: Dr. Alberto V. Tupas, Department of Pediatrics, College of Medicine, University of the Philippines, Manila, Philippines.
Secretary: Dr. Artemio P. Jongco, Department of Pediatrics, College of Medicine, University of the Philippines, Manila, Philippines.
Place: Philippine General Hospital. Time: Every two months.

SOUTH CAROLINA PEDIATRIC SOCIETY
President: Dr. B. Owen Ravenel, 95 Rutledge Ave., Charleston 16.
Secretary-Treasurer: Dr. John R. Harvin, 206 N. Sumter St., Sumter.

TENNESSEE PEDIATRIC SOCIETY
President: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Secretary-Treasurer: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Place: Chattanooga. Time: Second Monday in April.

TEXAS PEDIATRIC SOCIETY
President: Dr. John K. Glen, 4412 Montrose St., Houston.
Secretary-Treasurer: Dr. James N. Walker, 3616 Tulsa Way, Fort Worth 7.
Place: San Antonio. Time: Oct. 7-8, 1949.

VIRGINIA PEDIATRIC SOCIETY
President: Dr. C. P. Brown, 142 W. York St.. Norfolk.
Secretary: Dr. E. Berkeley Neal, 303 Washington Ave. S. W., Roanoke.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS
President: Dr. Thomas G. Folsom, 1139 Fourth Ave., Huntington.
Secretary: Dr. Warren J. Parsons, 425 Eleventh St., Huntington.

WISCONSIN STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS
Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary: Dr. L. M. Simonson, 1001 N. 8th St., Sheboygan.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION
Chairman: Dr. John Hart Davis, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Francis F. Silver, 9400 Euclid Ave., Cleveland.
Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS
President: Dr. A. L. Chute, 170 St. George St., Toronto, Canada.
Secretary: Dr. John Fletcher, 262 St. Clair St. W., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

BALTIMORE CITY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore.
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

BRONX PEDIATRIC SOCIETY

President: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Secretary: Dr. William A. Schonfeld, 211 W. 106th St., New York 25.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Walter R. Coles, 604–2d St., Brooklyn.
Secretary: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn 16.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

BUFFALO PEDIATRIC SOCIETY

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. T. Wood Clarke, 7 Cottage Place, Utica.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Tuesday of April and October.

CHICAGO PEDIATRIC SOCIETY

President: Dr. John L. Reichert, 1791 Howard St., Chicago 26.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

CINCINNATI PEDIATRIC SOCIETY

President: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Secretary: Dr. William F. Hunting, 6048 Montgomery, Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

DALLAS PEDIATRIC SOCIETY

President: Dr. Guy Hacker, 5711 Goliad St., Dallas.
Secretary-Treasurer: Dr. George R. Branch, 4325 Cole Ave., Dallas.
Place: Children's Hospital of Texas and Bradford Memorial Hospital. Time: 1 p. m., third Saturday and 8:30 p. m., the first Tuesday of each month.

DETROIT PEDIATRIC SOCIETY

President: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2.
Secretary: Dr. S. S. Bernstein, 650 Maccabees Bldg., Detroit.
Place: Variable. Time: Five times annually.

FORT WORTH PEDIATRIC SOCIETY

President: Dr. Frank Cohen, 712 S. Henderson, Fort Worth, Texas.
Secretary: Dr. H. H. Womack, 1422 Pennsylvania, Fort Worth, Texas.
Place: Welch and West Restaurant. Time: Third Friday of each month.

HONOLULU PEDIATRIC SOCIETY

President: Dr. Donald Marshall, Medical Group, Honolulu.
Secretary-Treasurer: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu

HOUSTON PEDIATRIC SOCIETY

President: Dr. Edward O. Fitch, 3720 Fannin St., Houston, Texas.
Secretary: Dr. Thomas J. Donovan, 3506 Sunset Blvd., Houston 5, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., last Tuesday of each month.

KANSAS CITY (MISSOURI) PEDIATRIC SOCIETY

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Hoel Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

KNOXVILLE-OAK RIDGE PEDIATRIC SOCIETY

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

LOS ANGELES COUNTY MEDICAL ASSOCIATION, PEDIATRIC SECTION

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn 16.
Secretary: Dr. Jacob J. Lichterman, 1433 Union St., Brooklyn 13.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. John Washington, 2032 Belmont Rd. N.W., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N.W. Time: Spring and fall.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. C. Barton Etter, 1678 Peach, Memphis 12, Tenn.
Secretary-Treasurer: Dr. Jacob Danciger, 188 S. Bellevue Blvd., Memphis 4, Tenn.
Place: University Center, 4 S. Dunlap. Time: 7 p. m., second Tuesday of every month.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. James Conway, 1721 E. Lake Bluff Blvd., Milwaukee 11, Wis.
Secretary-Treasurer: Dr. Walter Polacheck, 425 E. Wisconsin Ave., Milwaukee 2, Wis.
Place: City Club of Milwaukee. Time: Second Wednesday in February, April, June, October and December.

NASHVILLE PEDIATRIC SOCIETY

President: Dr. John M. Lee, Doctors Bldg., Nashville, Tenn.
Secretary: Dr. Dan S. Sanders Jr., 2103 Hayes St., Nashville, Tenn.
Time: Third Thursday of every month.

NEW YORK ACADEMY OF MEDICINE, SECTION ON PEDIATRICS

Chairman: Dr. John Dorsey Craig, 120 E. 75th St., New York 21.
Secretary: Dr. Morris Greenberg, 143 W. 87th St., New York.
Place: New York Academy of Medicine, 2 E. 103rd St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. Bertha M. Levy, 717 N. W. 22d St., Oklahoma City 3.
Secretary: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City 3.
Place: Oklahoma Club. Time: On call.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Milton Rapoport, 741 S. 3d St., Philadelphia.
Secretary: Dr. D. Stewart Polk, W. Montgomery Ave., Rosemont, Pa.
Place: College of Physicians, 19 S. 22nd St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. J. A. Gilmartin, 3708–15th Ave., Pittsburgh.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Municipal Hospital, Pittsburgh. Time: Second Friday in October, December, February and April.

QUEENS PEDIATRIC SOCIETY

Chairman: Dr. Walter C. A. Steffen, 42-28 Union St., Flushing, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 33-03 Parsons Blvd., Flushing, N. Y.
Place: Forest Hills, N. Y. Time: Third Monday of October, February, April; first Monday of December.

RICHMOND PEDIATRIC SOCIETY

President: Dr. Thomas S. Chalkley, 421 W. Grace St., Richmond 20, Va.
Secretary-Treasurer: Dr. John Paul Jones, 810 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

ROCHESTER PEDIATRIC SOCIETY

President: Dr. Jerome Glaser, 85 San Gabriel Dr., Rochester 10, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee.
Time: Third Friday of each month from October to May.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. Merl J. Carson, 500 S. Kingshighway, St. Louis.
Secretary-Treasurer: Dr. Jackson K. Eto, 734 Missouri Theatre Bldg., St. Louis 3.
Place: Hotel Branscome. Time: Second Thursday of each month from October to May, inclusive, 6:30 p. m.

SAN ANTONIO PEDIATRIC SOCIETY

President: Dr. Lucius Hill, 328 Medical Arts Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Bexar County Medical Library. Time: 7:30 p. m., first Tuesday of every month.

SEATTLE PEDIATRIC SOCIETY

President: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle 1.
Secretary: Dr. Jack M. Doctor, 738 Broadway, Seattle 22.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p. m.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. Harry F. Dietrich, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Clement H. Maloney, Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., second Wednesday in January, March, May, September and November.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. Ernest H. Watson, University Hospital, Ann Arbor.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor.

WACO PEDIATRIC SOCIETY

President: Dr. M. C. Carlisle, 1410 Austin Ave., Waco, Texas.
Secretary: Dr. F. W. Hoehn, 1422 Austin Ave., Waco, Texas.
Place: Provident Hospital, 1725 Colcord, Waco, Texas. Time: Third Thursday of each month.

WESTCHESTER COUNTY MEDICAL SOCIETY, PEDIATRICS SECTION (NEW YORK)

President: Dr. Harry W. Kaessler, 147 Prospect Ave., Mount Vernon, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Fourth Thursday of every other month from September to June (dinner meetings).